2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 1,4-dichlorobenzene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The

distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of 1,4-dichlorobenzene are indicated in Table 2-2 and Figure 2-2. Because cancer effects could occur at lower exposure levels, Figure 2-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for 1,4-dichlorobenzene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic

bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

Descriptive data are available from reports of humans exposed to 1,4-dichlorobenzene by inhalation (and possibly dermal contact). It is important to note that the case studies discussed in this section should be interpreted with caution since they reflect incidents in which individuals have reportedly been exposed to 1,4-dichlorobenzene, and they assume that there has been no other exposure to potentially toxic or infectious agents. There is usually little or no verification of these assumptions. Case studies in general are not scientifically equivalent to carefully designed epidemiological studies or to adequately controlled and monitored laboratory experiments. Thus, the case studies described below should be considered only as providing supplementary evidence that 1,4-dichlorobenzene may cause the reported effects.

2.2.1.1 Death

Only one report of human death attributed to 1,4-dichlorobenzene exposure has been located in the literature. A 60-year-old man and his wife died within months of each other due to acute yellow atrophy of the liver (also known as massive hepatic necrosis or fulminant hepatitis) (Cotter 1953). Their home had been "saturated" with 1,4-dichlorobenzene mothball vapor for a period of about 3-4 months, but no air measurements were available. Clinical symptoms included severe headache, diarrhea, numbness, clumsiness, slurred speech, weight loss (50 pounds in 3 months in the case of the husband), and jaundice. The wife died within a year of the initial exposure; however, it was not clear if 1,4-Dichlorobenzene was the primary cause of death. This case study did not address whether these individuals consumed excessive amounts of alcohol or had previous medical problems, such as a chronic liver infection.

Several studies were located regarding death in animals after inhalation exposure to 1,4-dichlorobenzene. In an acute-duration study, 2 of 6 male CD-l mice exposed to 1,4-dichlorobenzene at an air concentration

of 640 ppm, 6 hours a day for 5 days died on the fifth day; no deaths were reported at an exposure level of 320 ppm (Anderson and Hodge 1976).

Mortality data were also reported in intermediate-duration studies using rats, guinea pigs, and rabbits. In studies performed by Hollingsworth et al. (1956) rats, guinea pigs, and rabbits were exposed to 1,4-dichlorobenzene vapors for 9-12 weeks at an air concentration of 798 ppm, 8 hours a day, 5 days a week. In that study, 4 of 34 rats, 2 of 23 guinea pigs, and 4 of 16 rabbits died during the study period. The exact number of exposures that resulted in death was not specified.

In a chronic-duration study, there was no evidence of a treatment effect on mortality in Wistar rats exposed to 1,4-dichlorobenzene at concentrations up to 490-499 ppm for 5 hours a day, 5 days a week for 76 weeks (Riley et al. 1980).

LOAEL values for death in each species and duration category are listed in Table 2-l and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

The limited information available regarding systemic effects in humans and animals after inhalation exposure to 1,4-dichlorobenzene is discussed below. The highest NOAEL values and all reliable LOAEL values for these systemic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. A case of pulmonary granulomatosis was reported to have occurred in a 53-year-old woman who for 12-15 years had been inhaling 1,4-Dichlorobenzene crystals that were scattered on a weekly basis on the carpets and furniture of her home. A lung biopsy revealed the presence of 1,4-dichlorobenzene crystals with the surrounding lung parenchyma being distorted by fibrosis, thickening of the alveolar walls, and marked infiltrates of lymphocytes and mononuclear phagocytes. Also, there was some thickening of the muscular walls of small arteries and focal fibrous thickening of the pleura (Weller and Crellin 1953). These effects are most likely related to the physical interaction of 1,4-dichloro-benzene crystals (or any crystals when inhaled) with lung tissue, rather than to chemical toxicity. This conclusion by the authors of the study was based on exposure history of the patient, radiography, and

Table 2-1. Levels of Significant Exposure to 1,4-Dichlorobenzene - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
ACUTE EXPOSURE							
Systemic							
1	Rat (Alderley-Park)	10 d Gd 6-15 6 hr/d	Resp	508.4 F			Hodge et al. 1977
			Cardio	508.4 F			
			Hepatic	508.4 F			
			Renal	508.4 F			
			Bd Wt	508.4 F			
2	Rabbit (New Zealand)	13 d Gd 6-18 6 hr/d	Hepatic	800 F			Hayes et al. 1985
			Renal	800 F			
Reproductive							
3	Rat (Alderley-Park)	10 d Gd 6-15 6 hr/d		500 F			Hodge et al. 1977
4	Rat (NS)	16 d 5 d/wk 7 hr/d		173 M			Hollingsworth et al. 1956
5	Gn Pig (NS)	16 d 5 d/wk 7 hr/d		173 M			Hollingsworth et al. 1956
6	Rabbit (New Zealand)	13 d Gd 6-18 6 hr/d		800			Hayes et al. 1985

Table 2-1. Levels of Significant Exposure to 1,4-Dichlorobenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Developmental							
7	Rat (Alderley-Park)	10 d Gd 6-15 6 hr/d		508.4			Hodge et al. 1977
8	Rabbit (New Zealand)	13 d Gd 6-18 6 hr/d		300[b]	800 F (increased incidence of retroesophageal right subclavian artery)		Hayes et al. 1985
INTERMEDIATE EXPOSURE							
Death							
9	Rat (NS)	9-12 wk 5 d/wk 8 hr/d				798 (2/19 males and 2/15 females died)	Hollingsworth et al. 1956
10	Gn Pig (NS)	4-4.5 wk 5 d/wk 8 hr/d				798 M (2/16 died)	Hollingsworth et al. 1956
11	Rabbit (NS)	12 wk 5 d/wk 8 hr/d				798 (3 males and 1 female died)	Hollingsworth et al. 1956

Table 2-1. Levels of Significant Exposure to 1,4-Dichlorobenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Systemic							
12	Rat (NS)	2-12 wk 5 d/wk 7 or 8 hr/d	Resp	798 F		173 M (slight interstitial edema, alveolar hemorrhage)	Hollingsworth et al. 1956
			Cardio	173			
			Hepatic		173 F (slight liver congestion and granular degeneration)	798 (cloudy swelling and central necrosis)	
			Renal		173 (increased relative kidney weight)		
			Ocular		798 (eye irritation)		
			Bd Wt	173	798 (unquantitated weight loss)		
13	Rat (NS)	5.1-7.1 mo 5 d/wk 7 hr/d	Hemato	96			Hollingsworth et al. 1956
			Hepatic	96 [c]	158 (increased relative liver weight; cloudy swelling or degeneration of parenchyma)		
			Renal	96	158 M (increased relative kidney weight)		
			Bd Wt	341			

Table 2-1. Levels of Significant Exposure to 1,4-Dichlorobenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
14	Rat (Sprague-Dawley)	2 generation	Resp	211	538 (encrustation of the perinasal area)		Tyl and Neeper-Bradley 1989
			Hepatic	66.3 M 211 F	211 M (signif. incr. in liver wt.) 538 F		
			Renal	538 F	66.3 M (incr. incidence of hyaline droplets, tubular protein, granular cast formation, & interstitial nephritis in F_0 generation)		
			Ocular	211	538 (encrustation of periocular region; lacrimation)		
			Bd Wt	66.3 M 211 F	211 M (decr. body weight in the 538 F male F_0 group and in the F_1 male and females in the 5-week recovery study)		
			Other	211	538 (decreased grooming; unkempt appearance; decr. food consumption)		
15	Mouse (NS)	5.1-7.1 mo 5 d/wk 7 hr/d	Hepatic	158 M 96 F			Hollingsworth et al. 1956
			Renal	158 M 96 F			
			Bd Wt	158 M 96 F			

Table 2-1. Levels of Significant Exposure to 1,4-Dichlorobenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
16	Gn Pig (NS)	5.1-7.1 mo 5 d/wk 7 hr/d	Hepatic	96	158 F (increased relative liver weight)	341 (focal necrosis, slight cirrhosis in males)	Hollingsworth et al. 1956
			Renal	341			
			Bd Wt	96	158 (slight depression in final body weight)		
17	Gn Pig (NS)	2-4.5 wk 5 d/wk 7 or 8 hr/d	Resp		173 F (alveolar hemorrhage and edema)		Hollingsworth et al. 1956
			Cardio	798			
			Hepatic	173		798 (cloudy swelling in the liver and central necrosis)	
			Renal	798			
			Ocular	173	798 (eye irritation)		
			Bd Wt	173	798 (body weight loss, but not quantified)		
18	Rabbit (NS)	2-12 wk 5 d/wk 7 or 8 hr/d	Resp		173 F (lung congestion and interstitial edema)	798 (emphysema in 2/8)	Hollingsworth et al. 1956
			Hepatic	173		798 (cloudy swelling in the liver and central necrosis)	
			Renal	798			
			Ocular		798 (eye irritation; reversible nonspecific eye changes)		
			Bd Wt	173	798 (body weight depression, but not quantitated)		
Neurological							
19	Rat (NS)	9-12 wk 5 d/wk 8 hr/d				798 (tremors, weakness, unconsciousness)	Hollingsworth et al. 1956

Table 2-1. Levels of Significant Exposure to 1,4-Dichlorobenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
20	Gn Pig (NS)	4-4.5 wk 5 d/wk 8 hr/d					798	(tremors, weakness, unconsciousness)	Hollingsworth et al. 1956
21	Rabbit (NS)	12 wk 5 d/wk 8 hr/d					798	(tremors, weakness, unconsciousness)	Hollingsworth et al. 1956
	Reproductive								
22	Rat (NS)	5.1-7.1 mo 5 d/wk 7 hr/d		158 M					Hollingsworth et al. 1956
23	Rat (Sprague-Dawley)	2 generation		66.3	211	(decreased maternal body weight)	538	(decreased average litter size & survival)	Tyl and Neeper-Bradley 1989
24	Gn Pig (NS)	5.1-7.1 mo 5 d/wk 7 hr/d		158 M					Hollingsworth et al. 1956
	Developmental								
25	Rat (Sprague-Dawley)	2 generation		211			538	(decreased survival; decreased body weight)	Tyl and Neeper-Bradley 1989
	CHRONIC EXPOSURE								
	Systemic								
26	Human	4.75 yr	Resp		80M	(nose irritation)			Hollingsworth et al. 1956
			Hemato	725 M					
			Dermal	725 M					
			Ocular		80M	(eye irritation)			

Table 2-1. Levels of Significant Exposure to 1,4-Dichlorobenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)	Reference
27	Rat (Wistar)	76 wk 5 d/wk 5 hr/d	Resp	75	490-499	(increased lung weight at week 112)		Riley et al. 1980
			Cardio	75	490-499	(increased heart weight at week 112)		
			Gastro	490-499				
			Hemato	490-499				
			Musc/skel	490-499				
			Hepatic	75[d]	490-499	(incr. liver wt throughout the study in males; at wks 27 and 112 in females)		
			Renal	75	490-499	(incr. kidney wt. throughought study in males; at wks 27 & 112 in females)		
			Endocr	490-499				
			Ocular	490-499				
			Bd Wt	490-499				
			Other	490-499				

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an acute inhalation MRL of 0.8 ppm. Concentration adjusted for intermittent exposure, converted to an equivalent concentration in humans, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive an intermediate inhalation MRL of 0.2 ppm. Concentration adjusted for intermittent exposure, converted to an equivalent concentration in humans, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[d]Used to derive a chronic inhalation MRL of 0.1 ppm. Concentration adjusted for intermittent exposure, converted to an equivalent concentration in humans, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gd = gestational day; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to 1,4-Dichlorobenzene - Inhalation

Acute (≤14 days)

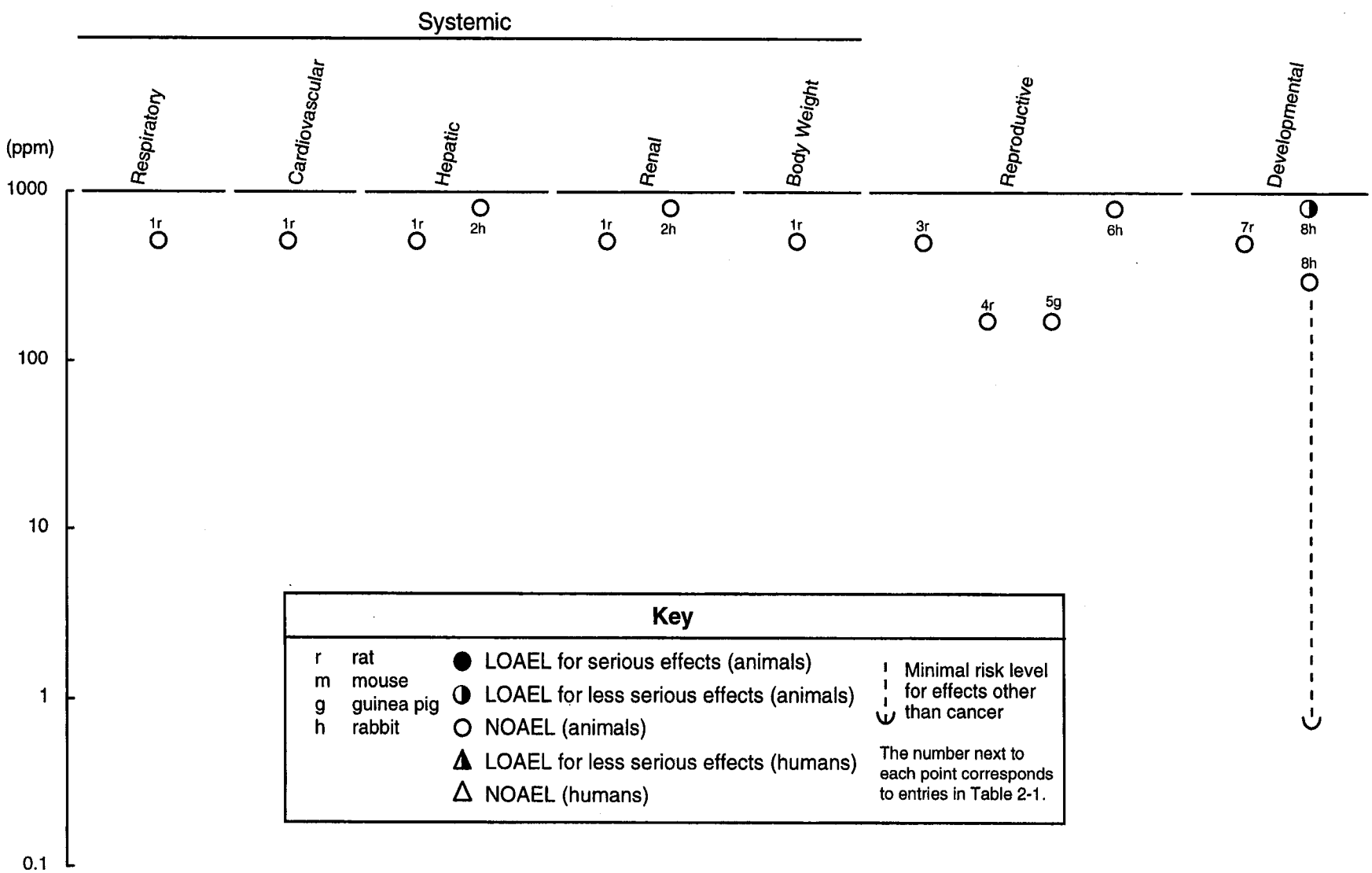


Figure 2-1. Levels of Significant Exposure to 1,4-Dichlorobenzene - Inhalation (cont.)

Intermediate (15-364 days)

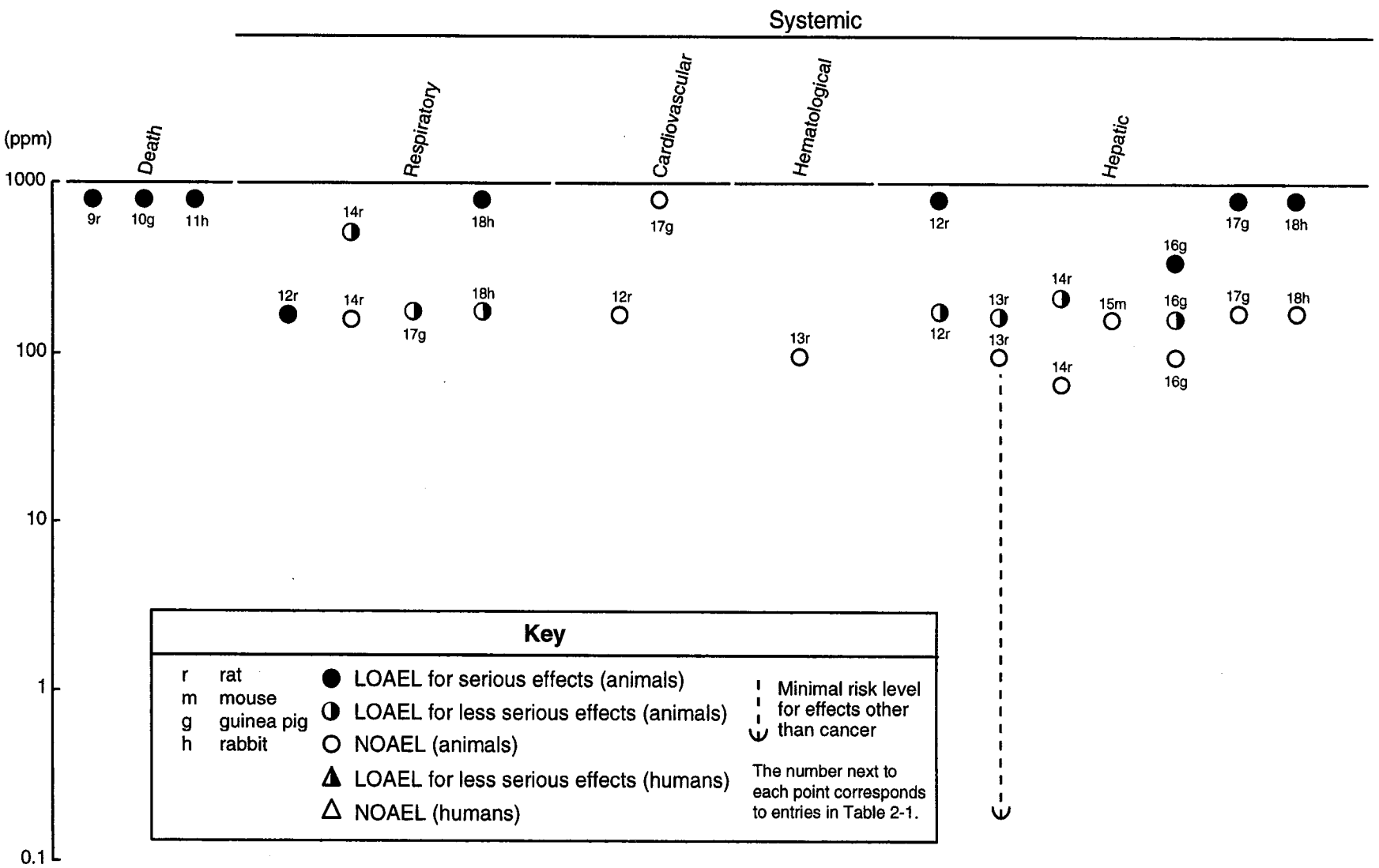


Figure 2-1. Levels of Significant Exposure to 1,4-Dichlorobenzene - Inhalation (cont.)

Intermediate (15-364 days)

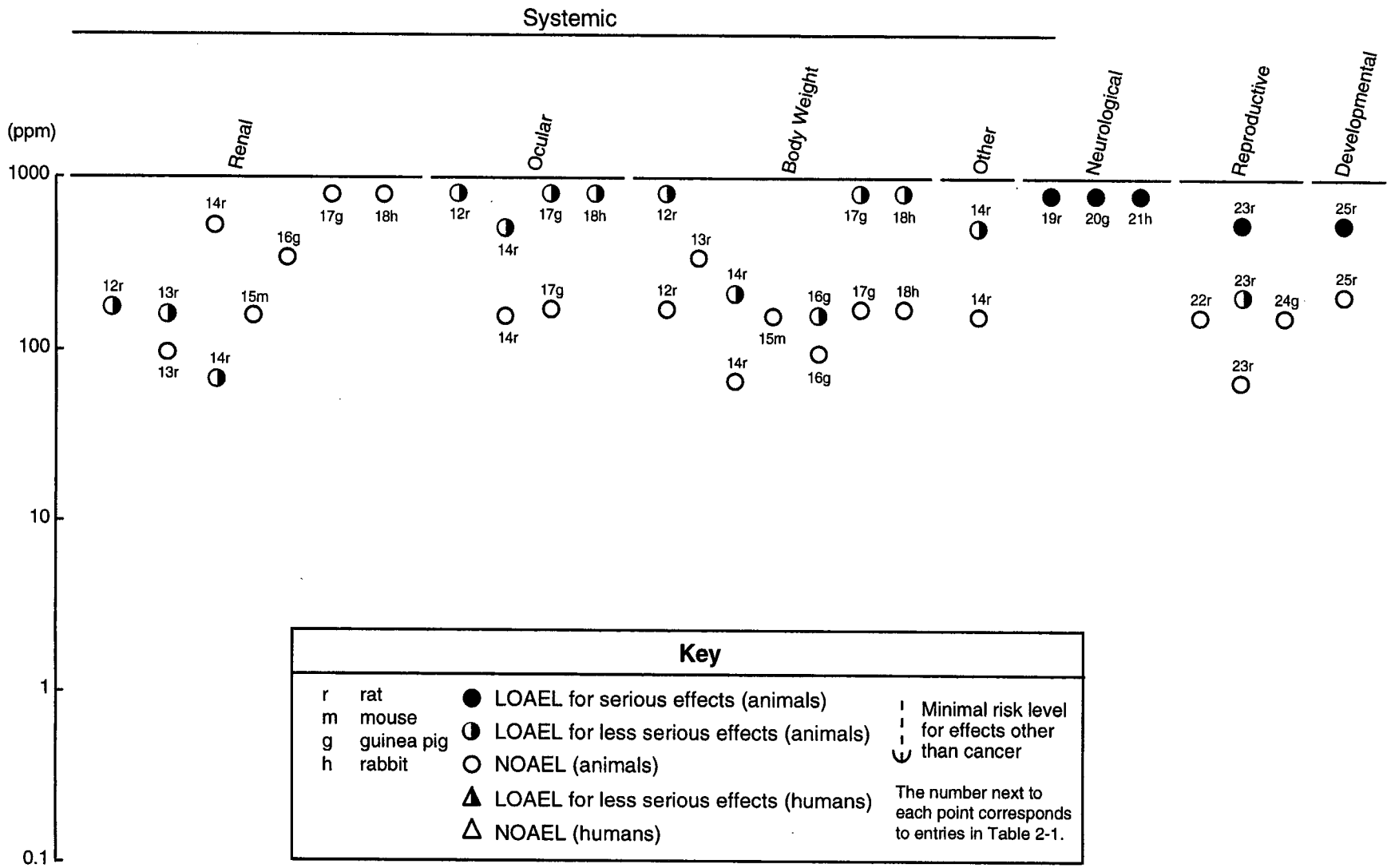
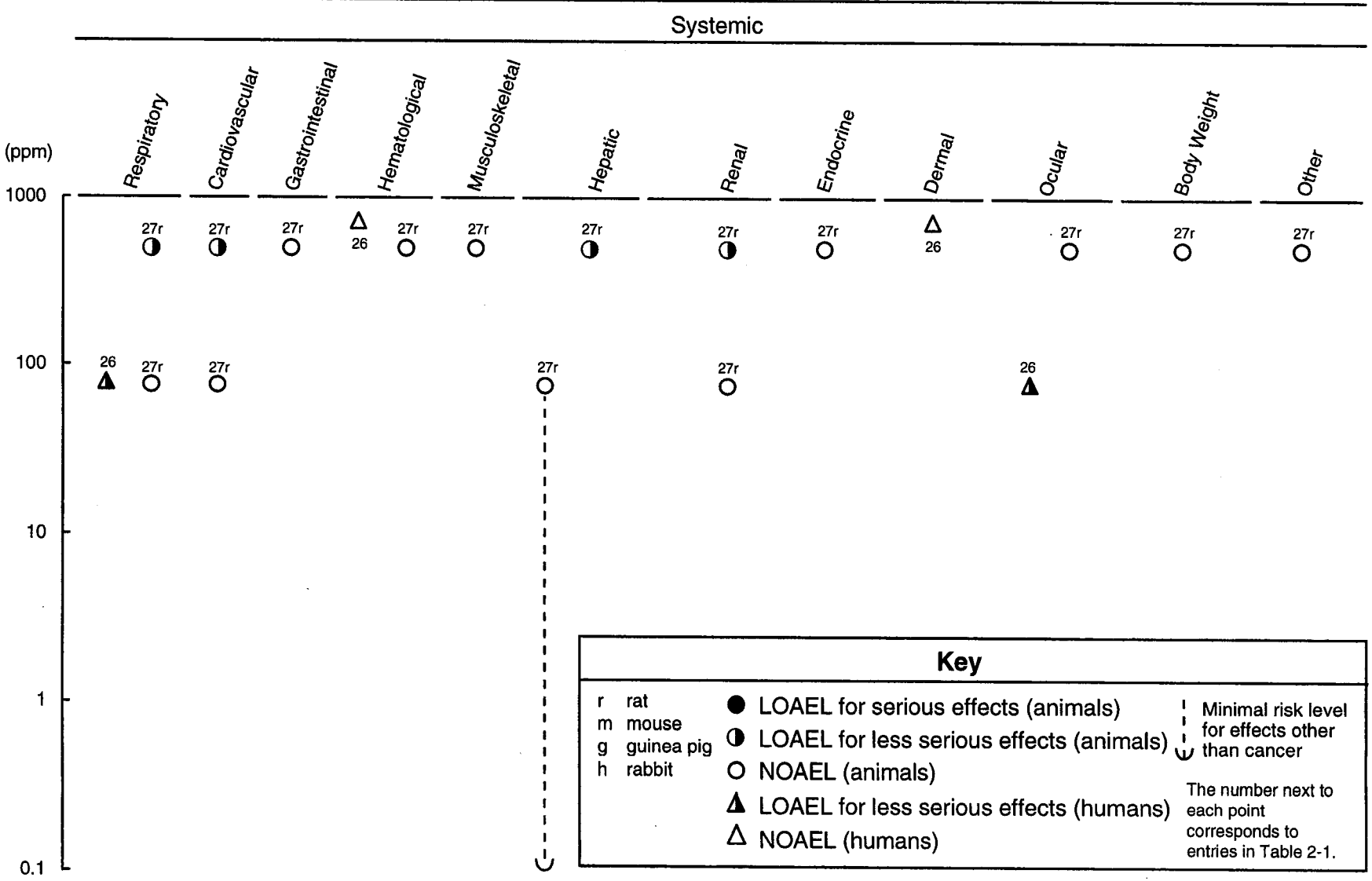


Figure 2-1. Levels of Significant Exposure to 1,4-Dichlorobenzene - Inhalation (cont.)

Chronic (≥365 days)



histological examination of the lung tissue which showed the presence of birefringent crystals and a clear granulatomous reaction. A study of 58 men occupationally exposed for 8 hours a day, 5 days a week, continually or intermittently, for 8 months to 25 years (average: 4.75 years) to 1,4-dichlorobenzene found painful irritations of the nose at levels ranging from 80 to 160 ppm. At levels greater than 160 ppm, the air was considered not breathable for unacclimated persons (Hollingsworth et al. 1956).

In pregnant Alderley-Park rats, whole-body exposure to 1,4-dichlorobenzene at air concentrations of 74.7, 198.6, or 508.4 ppm, 6 hours a day on gestation days (Gd) 6-15 produced no adverse clinical or pathological signs in the lung tissues of the dams (Hodge et al. 1977). Mild histopathological changes of interstitial edema, congestion, and alveolar hemorrhage were observed in the lungs of male (but not female) rats, female guinea pigs, and 1 female rabbit after 16 days of exposure to 1,4-dichlorobenzene at 173 ppm (Hollingsworth et al. 1956). Congestion and emphysema were also reported in the lungs of 2 rabbits exposed to 798 ppm for 12 weeks (Hollingsworth et al. 1956). These observations were derived from a large study using several species of laboratory animals; however, interspecies comparisons are difficult to make due to the various experimental designs used in this study. For example, at 798 ppm, 10 male rats, 15 female rats, 16 male guinea pigs, 7 female guinea pigs, and 8 rabbits of each sex were exposed up to 62 times; at 173 ppm, 5 rats of each sex, 5 guinea pigs of each sex, and 1 rabbit of each sex were exposed for 16 days. These reported observations provide only qualitative evidence of respiratory effects as a result of intermediate-duration inhalation exposure to 1,4-dichlorobenzene.

In a chronic-duration study, male and female Wistar rats were exposed to 1,4-dichlorobenzene at air concentrations of 75 or 490-499 ppm, 5 hours a day, 5 days a week for 76 weeks (Riley et al. 1980). Rats in the high-exposure group showed a small but significant increase in absolute lung weight at termination of the study (112 weeks). This response was not observed in rats sacrificed on week 76 or in rats exposed to 75 ppm 1,4-dichlorobenzene for 112 weeks. In addition, no treatment-related histological alterations were observed in the larynx, trachea, or lungs in this study.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to 1,4-dichlorobenzene.

Limited information is available regarding cardiovascular effects in animals. No alterations in relative heart weight were observed in rats or guinea pigs exposed to 1,4-dichlorobenzene at an air concentration of

173 ppm, 7 hours a day, 5 days a week for up to 12 exposures (Hollingsworth et al. 1956). Similar results were reported after approximately 130 exposures to 1,4-Dichlorobenzene at an air concentration of 96 ppm using the same exposure protocol (Hollingsworth et al. 1956); no other cardiovascular end points were evaluated in this study.

In pregnant Alderley-Park rats, whole-body exposure to 1,4-dichlorobenzene at air concentrations of 74.7, 198.6, or 508.4 ppm, 6 hours a day from Gd 6 to 15 produced no adverse clinical or pathological signs in the heart tissues of the dams (Hodge et al. 1977).

A significant increase in absolute heart weight was reported in male and female rats exposed to 1,4-dichlorobenzene at air concentrations of 490-499 ppm, 5 hours a day, 5 days a week for 76 weeks and allowed to recover until week 112 (Riley et al. 1980). This effect was not seen at the 76-week interim sacrifice or at the lower-exposure concentration of 75 ppm. Examination of the heart and aorta at interim sacrifices or at termination of the study revealed no significant histological alterations related to 1,4-dichlorobenzene treatment.

Gastrointestinal Effects. Two case reports provide evidence of gastrointestinal effects in humans after exposure to unknown concentrations of 1,4-dichlorobenzene. A 60-year-old man who had been exposed to vapors of 1,4-dichlorobenzene in his home for 3-4 months reported having several bowel movements a day with loose tarry stools for 10 days before being admitted to a hospital (Cotter 1953). The second case is that of a 34-year-old woman who had been exposed to vapors of 1,4-dichlorobenzene at work and became acutely ill with nausea and vomiting, and was hospitalized with hemorrhage from the gastrointestinal tract (Cotter 1953). The physical and chemical findings led to the diagnosis of subacute yellow atrophy and cirrhosis of the liver from 1,4-Dichlorobenzene exposure. No further information was located.

Limited information regarding gastrointestinal effects in animals is provided in a chronic-duration study. In that study (Riley et al. 1980), the investigators found no effect on the organ weight or on gross and histopathological appearance of the caecum, colon, duodenum, jejunum, esophagus, pancreas, and stomach in male and female Wistar rats exposed to 1,4-dichlorobenzene at air concentrations of up to 490-499 ppm, 5 hours a day, 5 days a week for 76 weeks.

Hematological Effects. Two reports of hematological effects in humans after inhalation exposure to 1,4-dichlorobenzene were located in the literature. Based on results from blood counts, anemia was diagnosed in two men; one had been exposed to unknown concentrations of 1,4-dichlorobenzene vapors at home for 3-4 months and the other had been in a storage plant saturated with 1,4-dichlorobenzene vapor. A woman exposed in a similar manner was diagnosed with borderline anemia (Cotter 1953). Early industrial hygiene surveys found no evidence of adverse hematological effects attributable to exposure to 1,4-dichlorobenzene in workers at air concentrations ranging from 10 to 550 ppm for 8 months to 25 years (average 4.75 years) (Hollingsworth et al. 1956).

Information regarding hematological effects in animals is scant. No hematologic effects (specific tests not provided) were observed in rats and rabbits exposed to 1,4-Dichlorobenzene vapors at concentrations of 96 or 158 ppm, respectively, dosed for durations of 7 hours a day, 5 days a week for 5-7 months (Hollingsworth et al. 1956). A chronic-duration study reported that some changes in blood chemistry and hematologic parameters were seen in rats exposed 5 hours per day, 5 days per week to 1,4-dichlorobenzene at air concentrations of up to 490-499 ppm for 76 weeks; however, the reported changes showed no consistent trend with dose, sex, or exposure duration that would indicate treatment-related effects (Riley et al. 1980).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to 1,4-dichlorobenzene.

One study was located which examined the musculoskeletal effects in laboratory animals after inhalation exposure to 1,4-dichlorobenzene. No gross or histological alterations in skeletal muscle (unspecified parameters) were detected in rats exposed to 1,4-dichlorobenzene at air concentrations of up to 490-499 ppm, 5 hours a day, 5 days a week for 76 weeks (Riley et al. 1980).

Hepatic Effects. Hepatic effects have been reported in humans following long-term exposure to 1,4-dichlorobenzene via inhalation. A 60-year-old man and his wife who were exposed to mothball vapor that “saturated” their home for 3-4 months both died of liver failure (acute liver atrophy) within a year of the initial exposure (Cotter 1953). Yellow atrophy and cirrhosis of the liver were reported in a 34-year-old woman who demonstrated 1,4-dichlorobenzene products in a department store and in a 52-year-old man who used 1,4-Dichlorobenzene occupationally in a fur storage plant for about 2 years (Cotter 1953).

Duration of exposure was not estimated for the 34-year-old woman, but was indicated in the report to be more than 1 year. No estimates of the 1,4-dichlorobenzene exposure levels (other than the use of the term "saturated") were provided in any of these reports, nor was it verified that 1,4-dichlorobenzene exposure was the only factor associated with the observed effects. History of alcohol consumption or prior liver disease factors were not mentioned for any of the cases reported by Cotter (1953). These case studies indicate that the liver is a target organ for 1,4-dichlorobenzene in humans, but they do not provide quantitative information.

In an acute-duration study using pregnant Alderley-Park rats, whole-body exposure to 1,4-dichlorobenzene at air concentrations of 74.7, 198.6, or 508.4 ppm, 6 hours a day from Gd 6 to 15 produced no adverse clinical or pathological signs in the hepatic tissues of the dams (Hodge et al. 1977). In a similar study, New Zealand White rabbits exposed whole-body to 1,4-dichlorobenzene 6 hours a day on Gd 6-l 8 experienced no adverse effects on absolute or relative maternal liver weights at air concentrations up to 800 ppm (Hayes et al. 1985).

In a cross-species comparative study, exposure to 1,4-dichlorobenzene at air concentrations up to 158 ppm, 7 hours a day, 5 days a week for 5-7 months produced no treatment-related effects on liver weight or microscopic appearance in male and female mice; in contrast, various hepatic effects were noted in rats, guinea pigs, and rabbits exposed to 1,4-dichlorobenzene at various levels and durations of exposure (Hollingsworth et al. 1956). There was considerable variability in the species of animals exposed at each dose, the number of animals exposed, and the total number of exposures. When rats and rabbits inhaled 173-798 ppm of 1,4-dichlorobenzene intermittently for 2-12 weeks, several hepatic effects were observed. Relative liver weight was increased in rats exposed to 173 ppm; histopathological examination at this exposure level revealed slight congestion and granular degeneration in female rats; at 798 ppm, liver changes included cloudy swelling and central necrosis in both sexes of rats and rabbits. In the same study, when rats inhaled 158-341 ppm 1,4-dichlorobenzene intermittently for 5-7 months, male and female rats displayed cloudy swelling and central zone degeneration of the hepatic parenchymal cells in the liver, and increased relative liver weights at 158 ppm. These changes were not seen at a concentration of 96 ppm. Based on the NOAEL of 96 ppm, an intermediate-duration MRL of 0.2 ppm was calculated as described in the footnote to Table 2-l and in Appendix A. In the same study, guinea pigs that were exposed to 341 ppm for a comparable duration or to 798 ppm for 2-4.5 weeks had focal necrosis and slight cirrhosis (in some animals) as well as hepatocyte swelling and degeneration.

In a 2-generation study of the effects of inhalation exposure to 1,4-Dichlorobenzene in Sprague-Dawley rats, males and females were exposed to 0, 66.3, 211, or 538 ppm 1,4-dichlorobenzene 6 hours a day for 10 weeks prior to mating. The females were also exposed during mating, and on Gd 0-19 and postnatal days 5-27; males were exposed throughout the study. Marked hepatocellular hypertrophy, localized in the centrilobular area, was noted in F_0 and F_1 males and females in the 538 ppm dose group; no such effects were seen in the low- and mid-dose groups. Liver weights were significantly elevated in F_0 males at the 211 and 538 ppm doses and in F_0 females at the 538 ppm dose; liver weights were also significantly elevated in F_1 males and females at the 538 ppm dose (Tyl and Neeper-Bradley 1989).

In a long-term inhalation study in rats, exposure to 1,4-Dichlorobenzene at air concentrations of 490-499 ppm 5 hours per day, 5 days per week for 76 weeks resulted in an increase in absolute liver weight throughout the study in males and at weeks 27 and 112 in females (Riley et al. 1980). This effect was not accompanied by histological alterations or by increased serum transaminase activities. No hepatic effects were noted at 75 ppm. None of the adverse hepatic effects reported at lower concentrations of 1,4-dichlorobenzene for shorter durations (Hollingsworth et al. 1956), as described above, were identified in the 76-week study. Based on the NOAEL of 75 ppm for lack of hepatic effects, a chronic-duration MRL of 0.1 ppm was calculated as described in the footnote to Table 2-1 and in Appendix A (Hollingsworth et al. 1956).

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to 1,4-dichlorobenzene.

In an acute-duration study using pregnant Alderley-Park rats, whole-body exposure to 1,4-dichlorobenzene at air concentrations of 74.7, 198.6, or 508.4 ppm, 6 hours a day from Gd 6 to 15 produced no adverse clinical or pathological signs in the kidney tissues of the dams (Hodge et al. 1977). In a similar study, pregnant New Zealand White rabbits exposed whole-body to 1,4-dichlorobenzene 6 hours a day on Gd 6-18 experienced no adverse effects with regard to either absolute or relative maternal kidney weights at air concentrations up to 800 ppm (Hayes et al. 1985).

In mice, rats, and rabbits exposed by inhalation to 1,4-dichlorobenzene at air concentrations ranging from 96 to 798 ppm, 7 or 8 hours per day, for periods as long as 7 months, no renal effects were noted in mice or rabbits, while both male and female rats experienced increased relative kidney weights at the 173 ppm

dose level. In addition, a slight cloudy swelling of the tubular epithelium was noted in female rats exposed to 798 ppm. In the same study, inhalation of 1,4-dichlorobenzene at 158 or 341 ppm intermittently for 5-7 months by rats caused a slight increase in relative kidney weight in males but not females (Hollingsworth et al. 1956). This effect was not observed in groups of guinea pigs, in one monkey, or in two rabbits under the same experimental conditions (Hollingsworth et al. 1956). The findings in this study are consistent with those reported by Riley et al. (1980) in a 76-week study in rats, described below.

In a 2-generation study of the effects of inhalation exposure to 1,4-dichlorobenzene in Sprague-Dawley rats, males and females were exposed to 0, 66.3, 211, or 538 ppm 1,4-dichlorobenzene 6 hours a day for 10 weeks prior to mating. The females were also exposed during mating, and on Gd 0-19 and postnatal days 5-27; males were exposed throughout the study. An increased incidence of nephrosis was seen in F_0 males of all dose groups and in F_1 males of the 211 and 538 ppm dose groups; lesions consisted of hyaline droplets, tubular protein nephrosis, granular cast formation, and interstitial nephritis. No renal lesions were noted in F_0 or F_1 females. Kidney weights were significantly elevated in F_0 males at all doses and in F_1 males at the 538 ppm dose. In females, kidney weights were significantly elevated in the F_0 generation at the 538 ppm dose, but were not elevated in the F_1 generation (Tyl and Neeper-Bradley 1989).

In a chronic-duration inhalation study in Wistar rats, exposure to 1,4-dichlorobenzene at air concentrations of 490-499 ppm, 5 hours a day, 5 days a week for 76 weeks resulted in an increase in absolute kidney weight in males throughout the study and in females at weeks 27 and 112 weeks. Exposure to 75 ppm 1,4-dichlorobenzene had no effect on kidney weight, and neither exposure level caused histopathological alterations in the kidneys (Riley et al. 1980). It is of interest to note that the renal effects observed in inhalation studies using 1,4-Dichlorobenzene are mild in contrast with the severe renal effects observed in oral studies as described in Section 2.2.2.2.

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to 1,4-dichlorobenzene.

The only information regarding endocrine effects in animals after inhalation exposure to 1,4-dichloro-benzene is from a chronic-duration study in rats. In that study (Riley et al. 1980), no gross or histopathological effects were observed in the adrenal, thyroid, or pituitary glands of male or female rats

exposed to 1,4-dichlorobenzene at air concentrations up to 490-499 ppm, 5 hours a day, 5 days a week for 76 weeks. No further information regarding endocrine effects was located.

Dermal Effects. Dermal effects resulting from 1,4-dichlorobenzene exposure were reported in a 69-year-old man who had been exposed for approximately 3 weeks to 1,4-Dichlorobenzene used in his home, including on a chair on which he had been sitting. He gradually developed petechiae (small red spots), purpura (purple or brownish-red spots), and swelling of his hands and feet. His sensitivity to 1,4-dichlorobenzene was established by an indirect basophil degranulation test which showed a strongly positive reaction (degenerative changes in 62% of his basophils when tested with 1,4-dichlorobenzene, compared with a 6% reaction of normal serum with 1,4-dichlorobenzene) (Nalbandian and Pearce 1965). The authors suggested that these effects were probably immunologically mediated. In a study of 58 men occupationally exposed to up to 725 ppm 1,4-Dichlorobenzene, 8 hours a day, 5 days a week continually or intermittently for 8 months to 25 years (average: 4.75 years), medical examinations revealed no evidence of dermatological effects (Hollingsworth et al. 1956).

No studies were located regarding dermal effects in animals after inhalation exposure to 1,4-dichlorobenzene.

Ocular Effects. In a report on 58 men who had worked for 8 months to 25 years (average exposure 4.75 years) in a plant that used 1,4-dichlorobenzene, painful irritation of the nose and eyes were reported at levels ranging from 80 to 160 ppm (Hollingsworth et al. 1956). At levels greater than 160 ppm, the air was considered unbreathable by unacclimated persons. Neither cataracts nor any other lens changes were found upon examination of their eyes.

There is no clear, quantitative evidence of ocular effects resulting from inhalation exposure to 1,4-dichlorobenzene in animal studies. Ocular effects, described as reversible, nonspecific eye ground changes (changes in the fundus or back of the eye), were seen in 2 rabbits exposed to 1,4-dichlorobenzene at 798 ppm 8 hours a day, 5 days a week for 12 weeks (Hollingsworth et al. 1956). In the same study, no lens changes were observed in rats or guinea pigs exposed to 798 ppm 1,4-dichlorobenzene, but eye irritation was reported in the three species tested. Ocular effects occurring during and/or after exposure to chemicals in air are likely to be due to direct contact of the chemical with the eye.

A chronic-duration inhalation study in male and female Wistar rats reported no histopathological alterations in the eyes of rats exposed to 1,4-dichlorobenzene at air concentrations up to 490-499 ppm, 5 hours a day, 5 days a week for 76 weeks (Riley et al. 1980). No further data were located.

Body Weight Effects. A 60-year-old man who was exposed to vapors of 1,4-dichlorobenzene in his home for 3& months was reported to have lost approximately 50 pounds in body weight in 3 months (Cotter 1953). His wife, who received similar exposure, also lost weight. A third case reported by the same author (Cotter 1953) is that of a 52-year-old man who was exposed to 1,4-Dichlorobenzene by using the chemical for preserving raw furs. On examination, this individual was described as being emaciated. Information regarding food consumption was not available in any of these cases. In the case of the 60-year-old man, persistent diarrhea may have contributed to the weight loss.

In an acute-duration study using pregnant Alderley-Park rats, whole-body exposure to 1,4-dichlorobenzene at air concentrations of 74.7, 198.6, or 508.4 ppm, 6 hours a day from Gd 6 to 15 had no effect on maternal body weight gain (Hodge et al. 1977).

Body weight data are available for various animal species after exposure to 1,4-dichlorobenzene 7-8 hours a day, 5 days a week, for periods ranging from 2 weeks to 6 months (Hollingsworth et al. 1956). Rats, rabbits, and guinea pigs experienced weight loss when exposed to 798 ppm, 8 hours a day, 5 days a week. Rats exposed to up to 341 ppm 1,4-dichlorobenzene for 5-7 months grew at a rate similar to that of unexposed controls. Similar results were obtained in rabbits exposed to 173 ppm for 16 days or to 158 ppm for about 200 days. Slight growth depression was observed in male and female guinea pigs exposed to 158 ppm 1,4-dichlorobenzene for 157 days, but only males showed a slight delay in growth when the exposure level was 341 ppm for 6 months. In male and female mice and in one female monkey there were no effects on body weight after exposure to 1,4-dichlorobenzene at air concentrations up to 158 ppm for as long as 7.1 months.

In a 2-generation study of the effects of inhalation exposure to 1,4-dichlorobenzene in Sprague-Dawley rats, males and females were exposed to 0, 66.3, 211, or 538 ppm 1,4-dichlorobenzene 6 hours a day for 10 weeks prior to mating. The females were also exposed during mating, and on Gd 0-19 and postnatal days 5-27; males were exposed throughout the study. Male F_0 body weight and body weight gain were significantly reduced in the 538 ppm group. Body weight gain was also significantly reduced in the

211 ppm group; however, the effect was seen at fewer observation periods. Female F_0 body weights were equivalent across all treatment groups during the entire prebreeding period. The F_1 generation males and females exposed to 538 ppm 1,4-dichlorobenzene had lower body weights than did controls; however, these decreases were accompanied by decreased food consumption (Tyl and Neeper-Bradley 1989).

A chronic-duration inhalation study in male and female Wistar rats found that body weight was not significantly altered after exposure to 1,4-Dichlorobenzene at air concentrations up to 490-499 ppm, 5 hours a day, 5 days a week for 76 weeks (Riley et al. 1980).

Other Systemic Effects. No studies were located regarding other effects in humans following inhalation exposure to 1,4-dichlorobenzene. Ascites, esophageal varices, hemorrhoids, and tarry stools are all secondary effects of subacute, yellow atrophy and cirrhosis of the liver (Cotter 1953).

A chronic-duration inhalation study in male and female Wistar rats found that food and water consumption was not significantly altered after exposure to 1,4-dichlorobenzene at air concentrations up to 490-499 ppm, 5 hours a day, 5 days a week for 76 weeks (Riley et al. 1980).

In a 2-generation study of the effects of inhalation exposure to 1,4-dichlorobenzene in Sprague-Dawley rats, males and females were exposed to 0, 66.3, 211, or 538 ppm 1,4-dichlorobenzene 6 hours daily for 10 weeks prior to mating. The females were also exposed during mating, and on Gd 0-19 and postnatal days 5-27; males were exposed throughout the study. Exposure of the F_0 and F_1 generations to 538 ppm 1,4-dichlorobenzene resulted in clinical signs of toxicity such as decreased grooming, unkempt appearance, decreased food consumption, and dehydration (Tyl and Neeper-Bradley 1989).

2.2.1.3 Immunological and Lymphoreticular Effects

As mentioned in Section 2.2.1.2, dermal effects observed in a 69-year-old man who had been exposed to 1,4-dichlorobenzene in his home for approximately 3 weeks (Nalbandian and Pearce 1965) may have been mediated by immunological mechanisms. In addition to petechiae, purpura, and swelling of his hands and feet, his serum showed a strong positive reaction to 1,4-dichlorobenzene in an indirect basophil degranulation test. The authors stated that, to their knowledge, this was the first reported case of allergic (anaphylactoid) purpura induced by exposure to 1,4-dichlorobenzene. Enlargement of the spleen was

reported in a woman who had been exposed to 1,4-dichlorobenzene in her home for 3-4 months and in a man who used 1,4-dichlorobenzene to preserve raw furs (Cotter 1953). This, however, was most likely a secondary response to hematological disturbances rather than an immunological effect.

A slight decrease in relative spleen weight was observed in male guinea pigs exposed to 1,4-dichlorobenzene at an air concentration of 173 ppm, 7 hours a day, 5 days a week for 16 days (Hollingsworth et al. 1956); no effect was seen in rats under the same experimental conditions. In a chronic-duration inhalation study, groups of male and female Wistar rats exposed to 1,4-Dichlorobenzene 5 hours a day, 5 days a week for 76 weeks exhibited no gross or hispathological alterations in the cervical, thoracic, and mesenteric lymph nodes; spleen; or thymus at air concentrations up to 500 ppm (Riley et al. 1980). No other immunological end points were evaluated.

2.2.1.4 Neurological Effects

Information regarding neurological effects in humans exposed to 1,4-dichlorobenzene via inhalation is limited to several case reports. A 60-year-old man whose home had been saturated with 1,4-dichlorobenzene mothball vapor for 3 or 4 months complained of persistent headache, numbness, clumsiness, and a burning sensation in his legs (consistent with peripheral nerve damage); he also showed slurred speech (Cotter 1953). In a more recent case study, a 25-year-old woman was exposed to high concentrations of 1,4-dichlorobenzene from her bedroom, bedding, and clothing. She had used this compound liberally as an insect repellant for 6 years. The subject sought medical assistance because of severe ataxia, speech difficulties, and moderate weakness of her limbs. Brainstem auditory-evoked potentials (BAEPs) showed marked delays of specific brainwave patterns. Her symptoms gradually improved over the next 6 months after cessation of exposure and the BAEPs examined 8 months later had returned to normal. This study suggests that there may be measurable but reversible neurological effects associated with human inhalation exposure to 1,4-dichlorobenzene (Miyai et al. 1988). The level of 1,4-dichlorobenzene exposure was neither known nor estimated in either of the human case studies. In addition, there is no certainty that exposure to 1,4-dichlorobenzene was the only factor associated with the toxic effects reported.

Neurological signs including marked tremors, weakness, and loss of consciousness were observed in rats, rabbits, and guinea pigs exposed to 798 ppm 1,4-dichlorobenzene 8 hours a day, 5 days a week (Hollingsworth et al. 1956). In a chronic-duration study in rats, exposure to up to 500 ppm 1,4-dichloro-

benzene 5 hours a day, 5 days a week for 76 weeks did not cause gross or histological alterations in the brain, sciatic nerve, or spinal cord, but absolute brain weight was slightly decreased at the termination of the study (Riley et al. 1980). Adult rats exposed 6 hours per day for 10 weeks to 538 ppm 1,4-dichlorobenzene during a 2-generation study displayed symptoms associated with compound neurotoxicity, including tremors, ataxia, and hyperactivity (Tyl and Neeper-Bradley 1989). The animals also decreased their grooming behavior and developed an unkempt appearance. At sacrifice, the relative brain weights of the males, but not the females, were significantly increased compared to the controls.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to 1,4-dichlorobenzene.

In an acute-duration study using pregnant Alderley-Park rats, whole-body exposure to 1,4-dichlorobenzene at air concentrations up to 508.4 ppm, 6 hours a day from Gd 6 to 15 did not adversely affect the number of implantations, resorptions, viable fetuses, corpora lutea, or sex ratios (Hodge et al. 1977). A similar study in inseminated New Zealand White rabbits exposed whole-body to 1,4-dichlorobenzene at air concentrations of 100, 300, or 800 ppm, 6 hours a day on Gd 6-18 found no differences between treated and control groups in the mean number of corpora lutea per dam, the mean number of implantation sites per dam the mean number of resorptions per litter, or the number of totally resorbed litters. At 300 ppm, there was a significant increase ($p<0.05$) in the percentage of resorbed implantations per litter and in the number of litters with resorptions; however, the results at 800 ppm were comparable to controls, and the percentage of litters with resorptions reported in the 300 ppm group was within the range reported for historical controls, suggesting this effect was not chemical- or dose-related (Hayes et al. 1985).

Exposure of rats and guinea pigs to 1,4-dichlorobenzene at an air concentration of 173 ppm, 7 hours a day, 5 days a week for 2 weeks did not significantly alter relative testis weight. The same results were obtained after intermittently exposing rats and guinea pigs to 1,4-dichlorobenzene at air concentrations up to 158 ppm for 5-7 months (Hollingsworth et al. 1956). There were no treatment-related effects on the

reproductive organs of male or female Wistar rats exposed to 1,4-Dichlorobenzene at concentrations up to 490-499 ppm, 5 hours a day, 5 days a week for 76 weeks (Riley et al. 1980). The evaluation of reproductive end points included organ weights and histopathology.

The effects of 1,4-dichlorobenzene vapors on the reproductive performance of Sprague-Dawley rats was assessed in a 2-generation study in which animals of both sexes were exposed before and during mating (Tyl and Neeper-Bradley 1989). The females were then exposed on Gd 0-19 and postnatal days 5-27. Effects on body weight, liver and kidney weight, and hepatocellular hypertrophy were found in the adult rats at exposure concentrations of 211 and 538 ppm and were indicative of toxicity to the breeding animals. These effects did not occur with the 66.3 ppm exposure concentration. Both generations of offspring exposed to the 538 ppm concentration had lower body weights than the controls at lactation day 4; average litter size and survival rates were decreased. When selected animals from the first filial generation were allowed to recover from the 1,4-dichlorobenzene exposure for a 5-week period, body weights of the 538 ppm exposure group remained lower than those for the controls. The authors concluded that parental toxicity was the cause of the increased risk to offspring rather than inherent effects of 1,4-dichlorobenzene on reproductive processes. In addition, no reduction in reproductive performance (as measured by the percentage of males successfully impregnating females) was observed in an inhalation study in which male mice were exposed to 1,4-dichlorobenzene at 75-450 ppm for 6 hours per day for 5 days before being mated with virgin females (Anderson and Hodge 1976). These data are consistent with the data from the males used in the 2-generation study discussed above.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 1.4-dichlorobenzene.

Exposure of pregnant Alderley-Park rats to 1,4-dichlorobenzene via inhalation at levels up to 508 ppm for 6 hours per day on Gd 6-15 did not result in developmental effects in the offspring (Hodge et al. 1977).

End points examined included the number of viable fetuses, fetal weight, litter weight, sex ratio, external abnormalities, and skeletal and visceral abnormalities.

In a 2-generation study of the effects of inhalation exposure to 1,4-dichlorobenzene in Sprague-Dawley rats, males and females who were exposed to 0, 66.3, 211, or 538 ppm 1,4-dichlorobenzene 6 hours daily for 10 weeks prior to mating were assessed. The females were also exposed during mating, and on Gd 0-19 and postnatal days 5-27; males were exposed throughout the study. F_1 and F_2 pup body weights in the 538 ppm group were significantly reduced from postnatal day 0 to 28. The number of F_1 and F_2 pups that died during the perinatal period was significantly elevated in the 538 ppm group (Tyl and Neeper-Bradley 1989).

The developmental effects of 1,4-dichlorobenzene have been evaluated in New Zealand White rabbits (Hayes et al. 1985). Pregnant rabbits were exposed to 1,4-dichlorobenzene by inhalation at 800 ppm for 6 hours per day on Gd 6-18. At 300 ppm, there was a significant increase in the number of litters with resorptions and the percentages of resorbed implantations per litter; however, this effect was not seen at 800 ppm and was thus probably not treatment-related. An increased incidence of retroesophageal right subclavian artery present in the offspring was noted; it was not considered to constitute a teratogenic response to exposure to 1,4-dichlorobenzene, but was considered only a minor variation. Based on the NOAEL of 300 ppm, an acute-duration MRL of 0.8 ppm was calculated as described in the footnote to Table 2-l and Appendix A (Hayes et al. 1985).

The highest NOAEL values and a reliable LOAEL value for developmental effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to 1,4-dichloro-benzene.

Cytogenetic studies have been conducted using bone marrow cells of rats following inhalation exposure to 1,4-Dichlorobenzene (Anderson and Richardson 1976). Three series of exposures were carried out: (1) one exposure at 299 or 682 ppm for 2 hours; (2) exposures at 75 or 500 ppm, 5 hours per day for 5 days; and

(3) exposures to 75 or 500 ppm, 5 hours per day, 5 days per week for 3 months. Bone marrow cells from both femurs were examined for chromosome or chromatid gaps, chromatid breaks, fragments, or other complex abnormalities. In all three experiments, exposure to 1,4-dichlorobenzene failed to induce any effects indicative of chromosomal damage. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans after inhalation exposure to 1,4-dichlorobenzene.

No evidence of carcinogenicity was observed in a long-term inhalation study in rats that were exposed to 1,4-Dichlorobenzene at 75 or 500 ppm intermittently for 76 weeks (Riley et al. 1980). The reported lack of extensive organ toxicity in this study (compared with results seen in oral studies described in Section 2.2.2.2) strongly suggests that a maximum tolerated dose (MTD) was not achieved in this study. In addition, a less-than-lifetime dosing regimen was used. These study design limitations prevent a reliable evaluation of the potential carcinogenicity of 1,4-Dichlorobenzene by inhalation.

2.2.2 Oral Exposure

Most of the data described in this section were derived from laboratory studies in which 1,4-dichlorobenzene was administered to test animals via gavage. In addition, two human case studies of 1,4-dichlorobenzene consumption are described. Case studies are not generally scientifically equivalent to well conducted epidemiologic studies or laboratory experiments and should be viewed only as providing contributory evidence that 1,4-dichlorobenzene may have caused the reported effects. These case studies do not provide unequivocal proof that 1,4-dichlorobenzene is solely responsible for the reported toxicological end points.

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to 1,4-dichlorobenzene.

Animal mortality data are available from acute-, intermediate-, and chronic-duration studies. In acute-duration animal studies, a single dose by gavage in olive oil of 1,000 mg/kg to rats and 1,600 mg/kg to guinea pigs resulted in no deaths, while a single dose of 4,000 mg/kg to rats and 2,800 mg/kg to guinea pigs resulted in 100% mortality (Hollingsworth et al. 1956). Similar results were seen in groups of adult male albino rats administered various doses of 1,4-dichlorobenzene in corn oil once daily for 14 days; administration of 1,4-dichlorobenzene at doses up to 600 mg/kg did not result in any deaths (Carlson and Tardiff 1976). Oral LD_{50} (lethal dose, 50% kill) values for adult Sherman rats administered 1,4-dichlorobenzene in peanut oil were calculated to be 3,863 and 3,790 mg/kg for males and females, respectively (Gaines and Linder 1986). In contrast, groups of male Fischer 344 rats (*n*=1/group) were administered 13-27,900 mg/kg body weight in corn oil via gavage. Twenty-four hours after dosing, the animals were weighed and exsanguinated. No mortality among the 1,4-dichlorobenzene-treated rats was observed (Allis et al. 1992).

In one series of studies (NTP 1987), the lethality data for 1,4-dichlorobenzene, when administered for 14 days by gavage in corn oil to Fischer 344 rats and $B6C3F_1$ mice, were rather inconsistent. In one of these studies, no 1,4-dichlorobenzene-related deaths occurred in rats of either sex that received doses up to 1,000 mg/kg/day; however, in the second rat study, 4 of 5 females (80%) at 1,000 mg/kg/day died, and all rats dosed at >2,000 mg/kg/day died. In one 14-day study in mice, no 1,4-dichlorobenzene-related deaths occurred in either sex at levels up to 1,000 mg/kg/day; however, in a second 14-day mouse study, 70% of mice at 1,000 mg/kg/day died, and all mice that received 4,000 mg/kg/day died within 4 days. At 1,200 mg/kg/day, 5 of 10 males and 1 of 10 females rats died. No deaths occurred at 600 mg/kg/day.

In 13-week gavage studies, 17 of 20 rats (8 of 10 males and 9 of 10 females) dosed with 1,4-dichlorobenzene in corn oil 5 days a week at 1,500 mg/kg/day died. When dosed in like manner with 1,200 mg/kg/day, 5 of 10 males and 1 of 10 females rats died. No deaths occurred at doses of 600 mg/kg/day or less (NTP 1987). Mortality rates in mice were somewhat lower; 8 of 20 (3 of 10 males and 5 of 10 females) animals dosed with 1,500 mg/kg/day 1,4-dichlorobenzene in corn oil 5 days a week died. No deaths occurred in males or females at doses up to 900 and 1,000 mg/kg/day, respectively (NTP 1987).

High mortality was reported in male rats that received 1,4-dichlorobenzene 5 days a week by gavage in corn oil in a 2-year study (NTP 1987). At 300 mg/kg/day, 26 of 50 males (52%) died; however, survival

of female rats at 600 mg/kg/day was comparable to controls. There was no excess mortality in mice of either sex that received 1,4-Dichlorobenzene 5 days a week by gavage in corn oil for 2 years at levels up to 600 mg/kg/day (NTP 1987). The high rate of mortality in male rats was probably related, in part, to the severe nephrotoxic effects and renal tumors that were reported in these animals and are described in more detail in Sections 2.2.2.2 and 2.2.2.8.

All reliable LOAEL values for lethality and LD_{50} values in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to 1,4-dichlorobenzene.

In a series of dose range-finding studies, groups of Fischer 344 rats were administered 1,4-Dichlorobenzene at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks (NTP 1987). At sacrifice, animals were examined grossly and major tissues were examined histologically. No compound-related effects were observed in the lungs at any dose up to 900 mg/kg/day, while rats treated with 1,200 mg/kg/day or higher exhibited epithelial necrosis of the nasal turbinates (NTP 1987). In parallel studies, $B6C3F_1$ mice were administered 1,4-dichlorobenzene at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks. No compound-related effects were observed in the lungs at any dose level (NTP 1987).

In 2-year exposure studies in Fischer 344 rats, no respiratory effects were reported in males or females that received 1,4-Dichlorobenzene by gavage in corn oil at levels up to 300 or 600 mg/kg/day, respectively (NTP 1987). In similarly dosed $B6C3F_1$ mice, no respiratory effects were reported in either sex at doses up to 600 mg/kg/day (NTP 1987).

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Fischer- 344)	once (GO)					Allis et al. 1992
2	Rat (Sherman)	once (GO)				3863 M (LD_{50}) 3790 F (LD_{50})	Gaines and Linder 1986
3	Rat (NS)	once (GO)				4000 (LD_{100})	Hollingworth et al. 1956
4	Rat (Fischer- 344)	14 d 1 x/d (GO)				2000 M (5/5 males died) 1000 F (4/5 females died)	NTP 1987
5	Mouse (B6C3F1)	14 d 1 x/d (GO)				4000 (10/10 deaths by day 4)	NTP 1987
6	Gn Pig (NS)	once (GO)				2800 (LD_{100})	Hollingsworth et al. 1956
	Systemic						
7	Rat (Fischer- 344)	once (GO)	Hemato	2790 M			Allis et al. 1992
			Hepatic		95 M (decreased relative liver weight)	475 M (centrilobular vacuolar degeneration)	
8	Rat (Wistar)	3 d 1 x/d (G)	Hepatic	250 F			Ariyoshi et al. 1975
			Bd Wt	250 F			

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
9	Rat (albino)	14 d 1 x/d (GO)	Hepatic	300 M	650 M	(6.5-fold increase in serum isocitrate dehydrogenase activity)	Carlson and Tardiff 1976
10	Rat (albino)	14 d 1 x/d (GO)	Hepatic		650 M	(decreased hexobarbital sleeping time; increased isocitrate dehydrogenase)	Carlson and Tardiff 1976
11	Rat (albino)	14 d 1 x/d (GO)	Hepatic	10 M	20 M	(increase in glucuronyl transferase and EPN detoxification activities)	Carlson and Tardiff 1976
12	Rat (Fischer- 344)	7 d 1 x/d (GO)	Renal		120 M	(protein droplet formation)	Charbonneau et al. 1987
13	Rat (Fischer- 344)	once (GO)	Renal	500 F	500 M	(increase in protein droplet formation)	Charbonneau et al. 1987
14	Rat (Fischer- 344)	once (GO)	Hepatic		600 F	(increased liver weight)	Eldridge et al. 1992
			Bd Wt	600 F			
15	Rat (Fischer- 344)	once (GO)	Hepatic		600 F	(centrilobular hepatocyte vacuolation)	Eldridge et al. 1992
16	Rat (Fischer- 344)	1 wk 5 d/wk 1x/d (GO)	Hepatic	25 M	75 M	(increased microsomal 7-pentoxyresorufin O-dependentylase activity)	Lake et al. 1997
			Renal	300 M			
			Bd Wt	150 M	300 M	(approx. 10% decr. body weight gain)	
17	Rat (Fischer- 344)	14 d 1x/d (GO)	Bd Wt	500 M 1000 F	1000 M	(7-12% decrease in final body weight)	NTP 1987

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
18	Rat (Fischer- 344)	14 d 1x/d (GO)	Bd Wt	500	1000 (13.5% reduction in final body weight in males, 16.7% in females)		NTP 1987
19	Rat (albino)	5 d 1x/d (G)	Hepatic			770 M (porphyria; degeneration of hepatocytes; focal necrosis)	Rimington and Ziegler 1963
			Bd Wt	770 M			
			Other		770M (loss of appetite)		
20	Rat (albino)	5 d 1 x/d (G)	Hepatic			850 M (porphyria; degeneration of hepatocytes; focal necrosis)	Rimington and Ziegler 1963
21	Mouse (B6C3F1)	once (GO)	Hepatic		600 (increased liver weight)		Eldridge et al. 1992
			Bd Wt	600			
22	Mouse (B6C3F1)	once (GO)	Hepatic		600 (centrilobular hepatocyte vacuolation)		Eldridge et al. 1992
23	Mouse (B6C3F1)	1 wk 5 d/wk 1x/d (GO)	Hepatic		300M (increased relative liver weight)		Lake et al. 1997
			Renal	600 M			
			Bd Wt	600 M			
24	Mouse (B6C3F1)	14 d 1 x/d (GO)	Bd Wt	1000			NTP 1987
25	Mouse (B6C3F1)	14 d 1 x/d (GO)	Bd Wt		250M (13.3% reduction in final body weight)		NTP 1987

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL: Less serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference
26	Mouse (B6C3F1)	4 d 1 x/d (GO)	Hepatic		300 (increased liver weight and hepatocyte proliferation)		Umemura et al. 1992
			Renal	600			
27	Mouse (B6C3F1)	Once	Hepatic	1000 M	1800 M (increased ALT activity; severe centrilobular hepatocyte swelling)		Umemura et al. 1996.
28	Mouse (B6C3F1)	Once	Hepatic		1800 M (increased ALT activity; increased BrdU labeling)		Umemura et al. 1996.
	Neurological						
29	Rat (albino)	5 d 1 x/d (G)				770 M (clonic contractions; slight tremors; hemiparesis)	Rimington and Ziegler 1963
	Reproductive						
30	Rat (CD)	10 d Gd 6-15 1 x/d (GO)		1000 F			Giavini et al. 1986
	Developmental						
31	Rat (CD)	10 d Gd 6-15 1 x/d (GO)		250	500 (extra rib in fetuses)		Giavini et al. 1986
	INTERMEDIATE EXPOSURE						
	Death						
32	Rat (Fischer- 344)	13 wk 5 d/wk (GO)				1200 M (5/10 males died) 1500 F (9/10 females died)	NTP 1987

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
33	Mouse (B6C3F1)	13 wk 5 d/wk (GO)				1500 (3/10 males and 5/10 females died)	NTP 1987
	Systemic						
34	Rat (Fischer- 344)	13 wk 5 d/wk (GO)	Hepatic		600 (increased liver weight; hypertrophic centrilobular hepatocytes)		Eldridge et al. 1992
			Bd Wt	600			
35	Rat (NS)	192 d 5 d/wk (GO)	Hemato	188 F			Hollingsworth et al. 1956
			Hepatic		188[b] F (slight increase in liver weight, but not quantified)	376 F (slight cirrhosis, focal necrosis)	
			Renal		188 F (slight increase in kidney weight, but not quantified)		
			Ocular	376 F			
36	Rat (Fischer- 344)	4 or 13 wk 5 d/wk 1x/d (GO)	Hepatic	25 M	75M (increased relative liver weight, induction of microsimal P450 and 7-pentoxyresorufin O-depentylase activity)		Lake et al. 1997
			Renal	75 M	150M (increased relative kidney weight)		
			Bd Wt	75 M	150M (approx. 10% decreased body weight gain)		

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
37	Rat (Fischer- 344)	13 wk 5 d/wk (GO)	Resp	600			NTP 1987
			Cardio	600			
			Gastro	600			
			Musc/skel	600			
			Hepatic	600			
			Renal	300 M 600 F	600M (moderate tubular degeneration in 9/10)		
			Endocr	600			
			Dermal	600			
			Ocular	600			
			Bd Wt	600			

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL: Less serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference
38	Rat (Fischer- 344)	13 wk 5 d/wk (GO)	Resp	900	1200 (epithelial necrosis of nasal turbinates)		NTP 1987
			Cardio	1500			
			Gastro	900		1200 (epithelial necrosis of small intestine mucosa)	
			Hemato	300 F	300 M, 600 F (slight decreases in red blood cell count, hematocrit, and hemoglobin concentration)		
			Musc/skel	1500			
			Hepatic	300 M, 900 F	600 M (significant increase in serum cholesterol)	1200 (degeneration and necrosis of hepatocytes)	
			Renal	1500 F		300 M (necrosis of renal cortical tubular epithelium)	
			Endocr	1500			
			Dermal	1500			
			Ocular	900 M, 1200 F	1200 M, 1500 F (ocular discharge)		
			Bd Wt	900 F	300 M, 1200 F (11% decrease in final body weight)	1500 M (final body weight reduced by 20-32%)	
39	Mouse (B6C3F1)	13 wk 5 d/wk (GO)	Hepatic	300	600 (increased liver weight; hypertrophic centrilobular hepatocytes)		Eldridge et al. 1992
			Bd Wt	600			
40	Mouse (B6C3F1)	4 or 13 wk 5 d/wk 1x/d (GO)	Hepatic		300 M (increased relative liver weight; induction of microsomal 7-pentoxyresorufin O-depentylase activity)	600 M (marked centrilobular hypertrophy, induction of microsomal cytochrome P450)	Lake et al. 1997
			Renal	600 M			
			Bd Wt	600 M			

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
41	Mouse (B6C3F1)	13 wk 5 d/wk (GO)	Resp	1800			NTP 1987
			Cardio	1800			
			Gastro	1800			
			Hemato	1800 F	600 M (34% reduction in WBC count)		
			Musc/skel	1800			
			Hepatic		600 (hepatocellular degeneration in 7/10 males and 9/10 females)		
			Renal	1800			
			Endocr	1800			
			Dermal	1800			
			Ocular	1800			
			Bd Wt		600 (final body weight reduced 13.9% in males and 10.3% in females)		

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
42	Mouse (B6C3F1)	13 wk 5 d/wk (GO)	Resp	900			NTP 1987
			Cardio	900			
			Gastro	900			
			Hemato	900			
			Musc/skel	900			
			Hepatic	338	675 (moderate hepatocytomegaly in 9/10 males and 10/10 females)		
			Renal	900			
			Endocr	900			
			Dermal	900			
			Ocular	900			
			Bd Wt	900			
	Immunological/Lymphoreticular						
43	Rat (Fischer- 344)	13 wk 5 d/wk (GO)		900		1200 (lymphoid depletion of thymus and spleen)	NTP 1987
44	Mouse (B6C3F1)	13 wk 5 d/wk (GO)		1000		1500 (lymphoid necrosis in thymus; lymphoid depletion in the spleen; hematopoietic hypoplasia in spleen and bone marrow)	NTP 1987
	Neurological						
45	Rat (Fischer- 344)	13 wk 5 d/wk (GO)		900 M 1200 F		1200 M 1500 F (tremors, poor motor response)	NTP 1987

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less serious (mg/kg/day)		Serious (mg/kg/day)	
	Reproductive							
46	Rat (Fischer- 344)	13 wk 5 d/wk (GO)		1500				NTP 1987
47	Mouse (B6C3F1)	13 wk 5 d/wk (GO)		1000 F 1800 M	1500 F	(increase in relative ovary weight)		NTP 1987
	CHRONIC EXPOSURE							
	Death							
48	Rat (Fischer- 344)	2 yr 5 d/wk (GO)					300 M (26/50 compound-related deaths)	NTP 1987

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL				Reference
					Less serious (mg/kg/day)		Serious (mg/kg/day)		
	Systemic								
49	Rat (Fischer- 344)	2 yr 5 d/wk (GO)	Resp	300 M 600 F					NTP 1987
			Cardio	300 M 600 F					
			Gastro	300 M 600 F					
			Hemato	300 M 600 F					
			Musc/skel	300 M 600 F					
			Hepatic	300 M 600 F					
			Renal		150 M	(moderate nephropathy)	300	(increased severity of the nephropathy)	
			Endocr	600 F	150 M	(increased incidence of parathyroid hyperplasia)			
			Dermal	300 M 600 F					
			Ocular	300 M 600 F					
			Bd Wt	150 M 300 F	300 M 600 F	(12.5% decrease in body weight gain) (12.4% decrease in body weight gain)			

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL				Reference
					Less serious (mg/kg/day)		Serious (mg/kg/day)		
50	Mouse (B6C3F1)	2 yr 5 d/wk (GO)	Resp	600					NTP 1987
			Cardio	600					
			Gastro	600					
			Hemato	600					
			Musc/skel	600					
			Hepatic		300	(hepatocellular degeneration, hepatocyte swelling and vacuolation)			
			Renal				300	(nephropathy, degeneration of cortical tubular epithelium)	
			Endocr	600 F	300 M	(follicular cell hyperplasia in thyroid; adrenal medullary hyperplasia; focal hyperplasia of adrenal gland capsule)			
			Dermal	600					
			Ocular	600					
			Bd Wt	600					
	Immunological/Lymphoreticular								
51	Rat (Fischer- 344)	2 yr 5 d/wk (GO)		600					NTP 1987
52	Mouse (B6C3F1)	2 yr 5 d/wk (GO)			300	(increased incidence of lymphoid hyperplasia of lymph nodes)			NTP 1987

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)		
	Neurological							
53	Rat (Fischer- 344)	2 yr 5 d/wk (GO)		600				NTP 1987
54	Mouse (B6C3F1)	2 yr 5 d/wk (GO)		600				NTP 1987
	Reproductive							
55	Rat (Fischer- 344)	2 yr 5 d/wk (GO)		600				NTP 1987
56	Mouse (B6C3F1)	2 yr 5 d/wk (GO)		600				NTP 1987
	Cancer							
57	Rat (Fischer- 344)	2 yr 5 d/wk (GO)				300 M	(CEL: increased incidence of combined renal tubular cell adenocarcinoma and adenoma)	NTP 1987

Table 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL				Reference
					Less serious (mg/kg/day)		Serious (mg/kg/day)		
58	Mouse (B6C3F1)	2 yr 5 d/wk (GO)					600	(CEL: increased incidence of hepatocellular carcinomas and adenomas)	NTP 1987

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate oral minimal risk level (MRL) of 0.4 mg/kg/day; dose divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans and 10 for human variability).

ALT = alanine aminotransferase; Bd Wt = body weight; BrdU = bromodeoxyuridine; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; EPN = O-ethyl-O-nitrophenul phenylphosphorothionate; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestatinal day; (GO) = gavage in oil; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LD_{100} = lethal dose, 100% kill; LOAEL = lowest-observable-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; wk = week(s); x = times; yr = year(s)

Figure 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral

Acute (≤14 days)

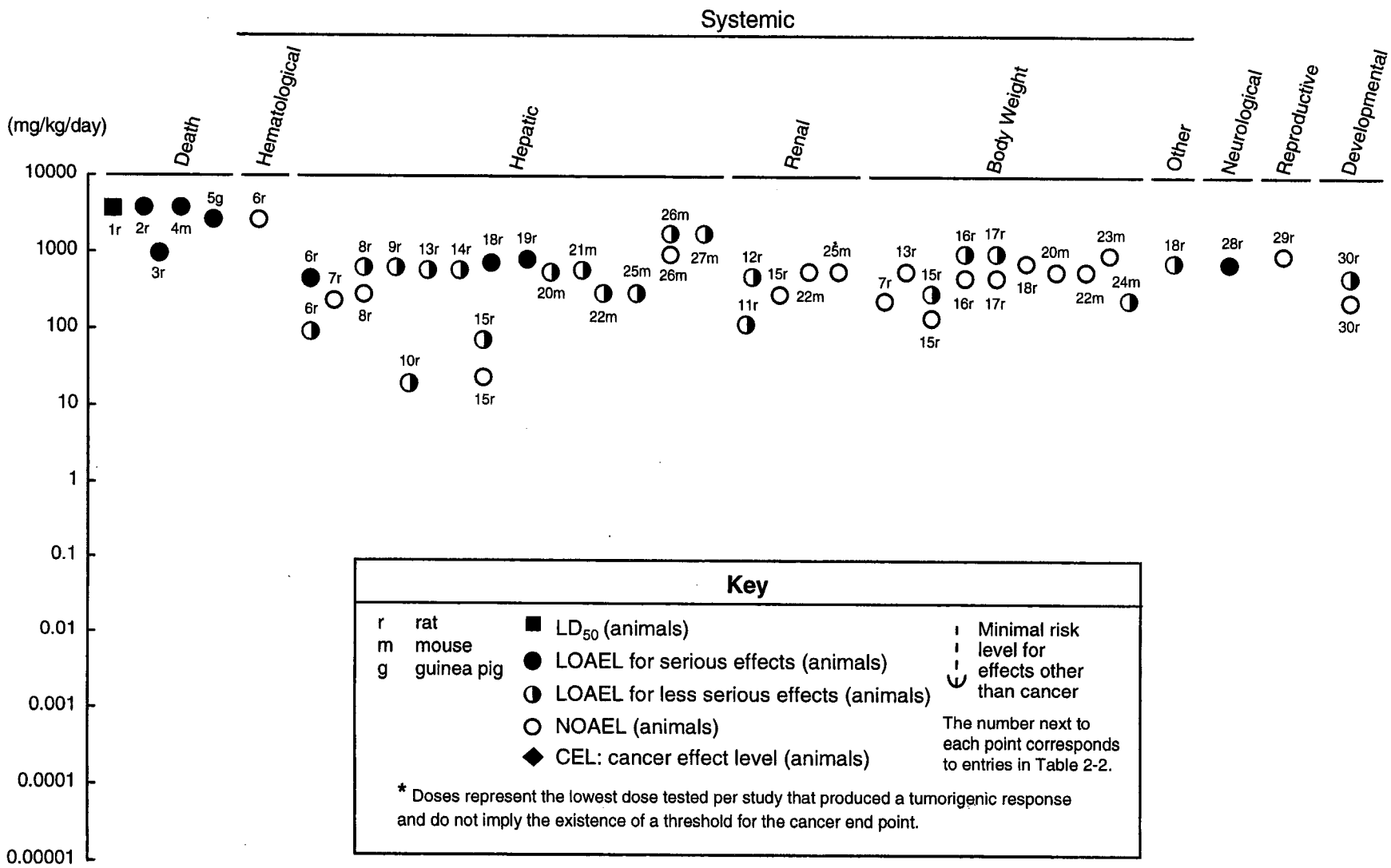


Figure 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (cont.)

Intermediate (15-364 days)

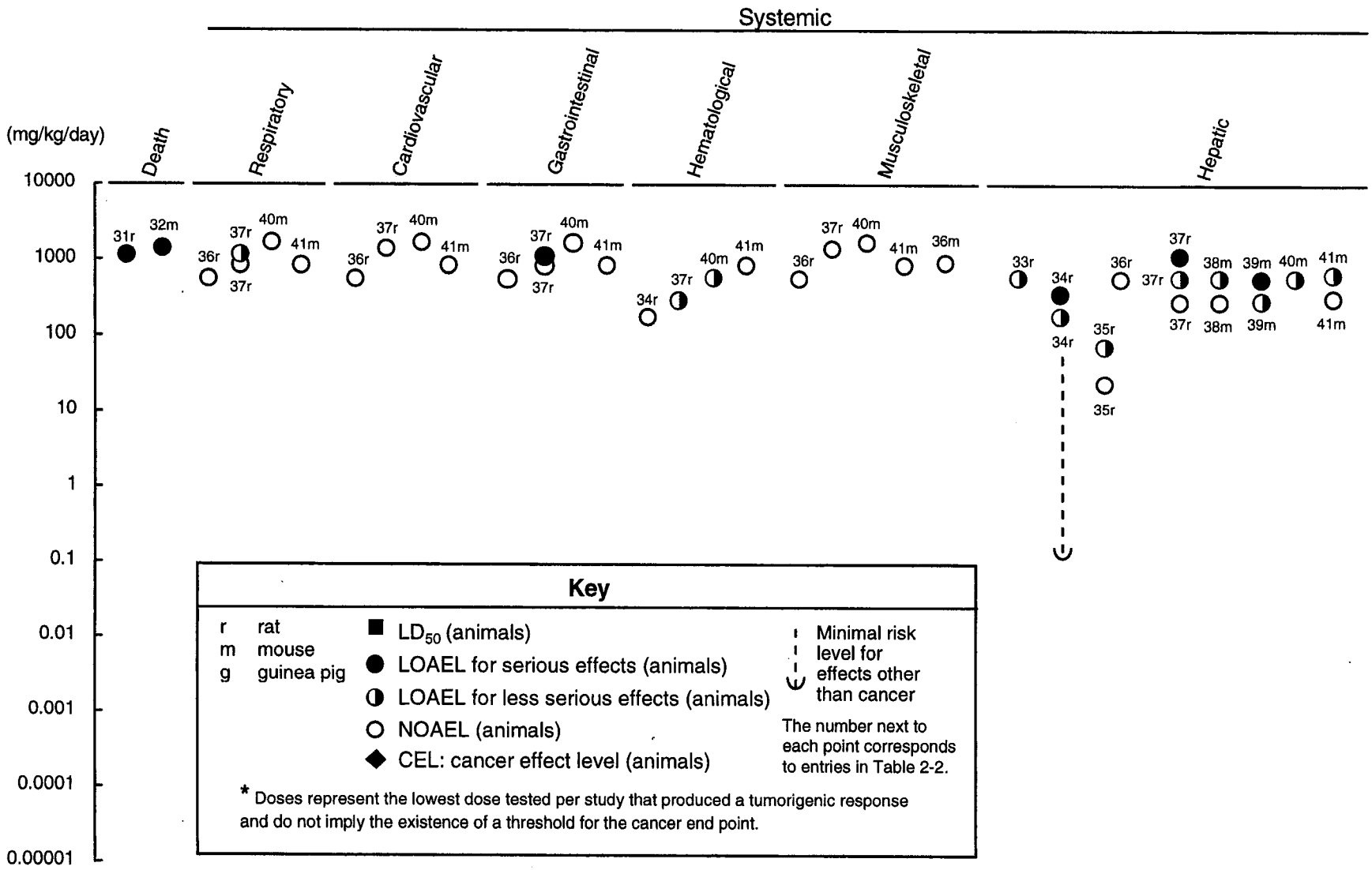


Figure 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (cont.)

Intermediate (15-364 days)

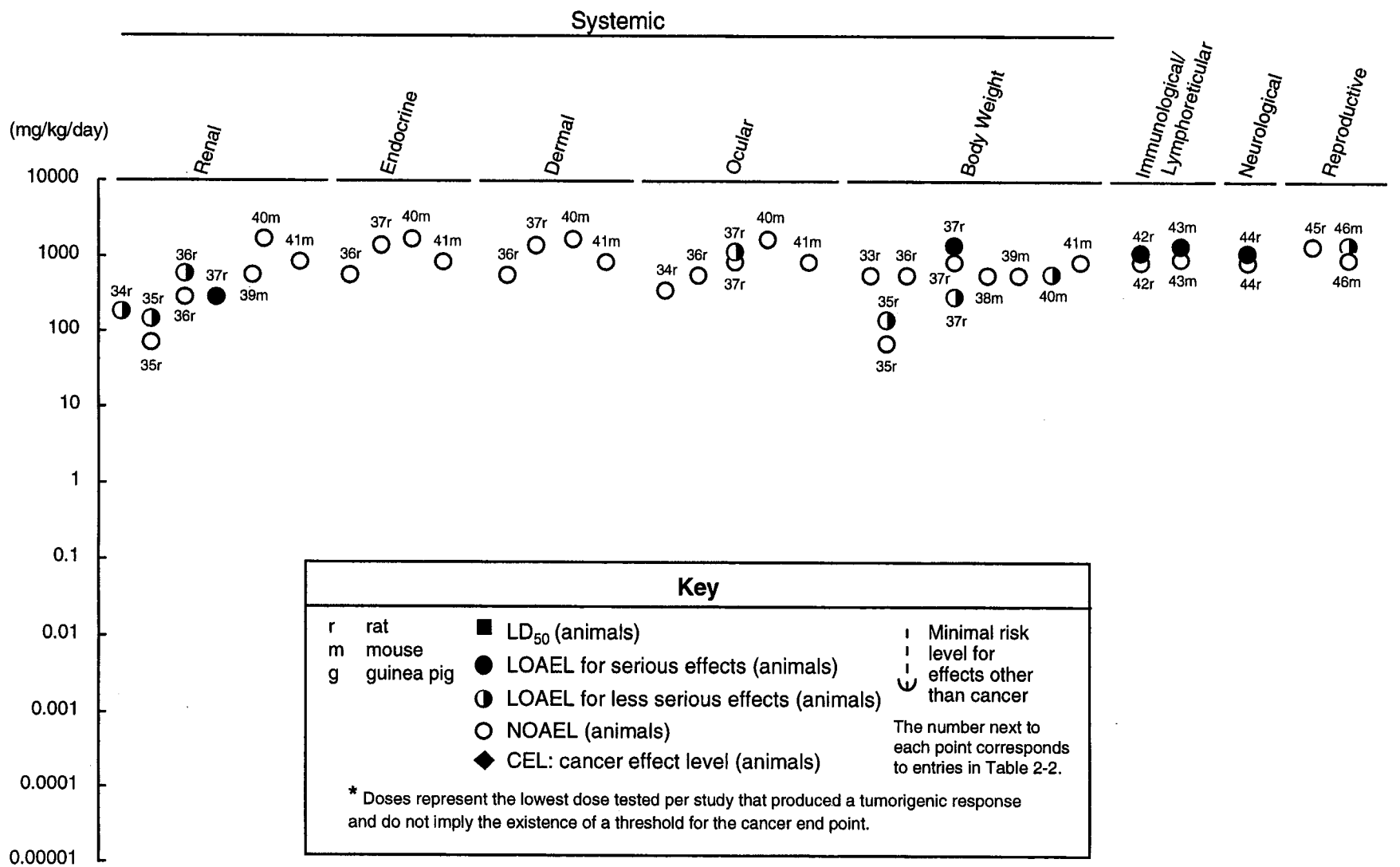
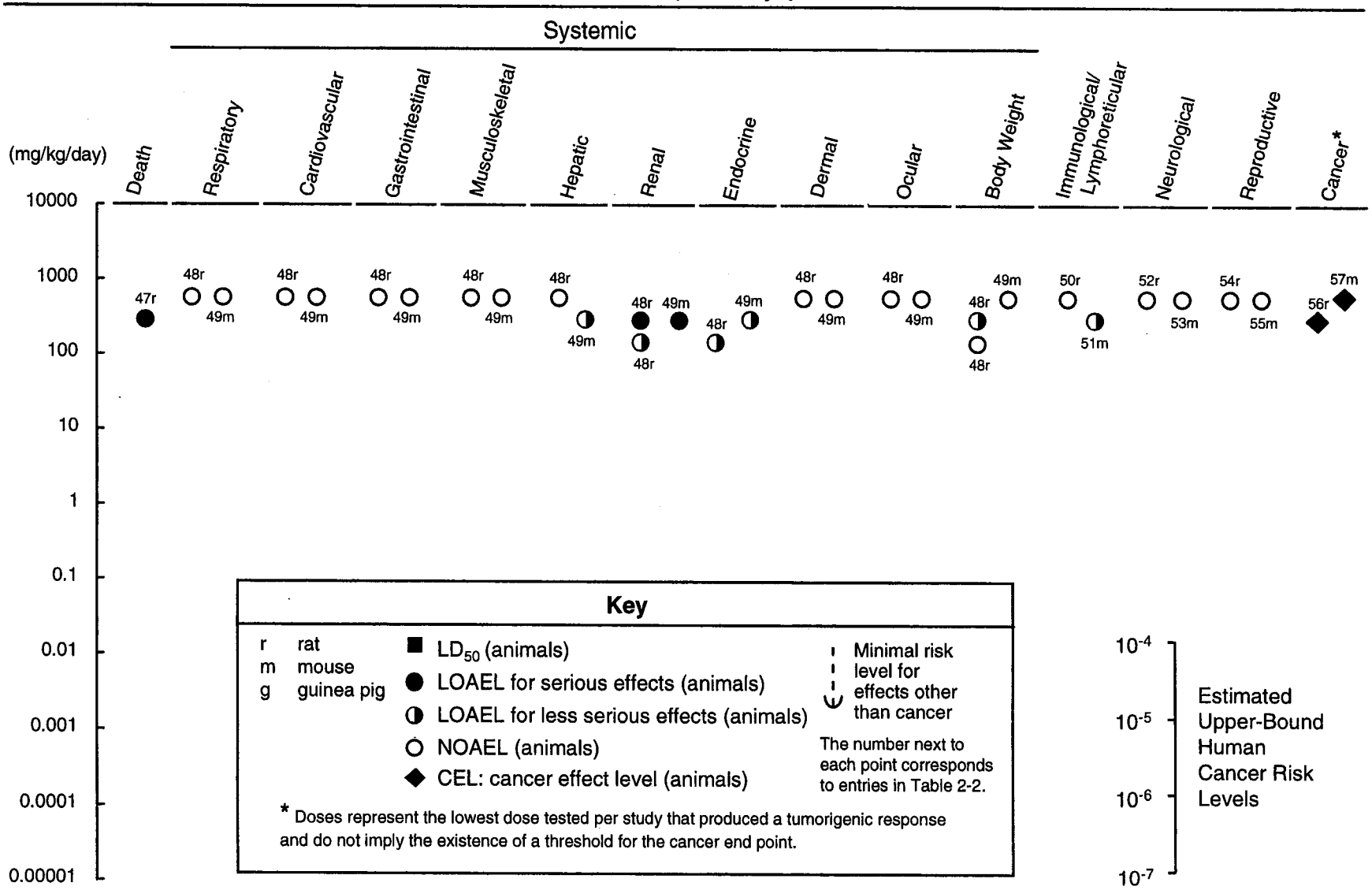


Figure 2-2. Levels of Significant Exposure to 1,4-Dichlorobenzene - Oral (cont.)

Chronic (≥365 days)



Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to 1,4-dichlorobenzene.

In a series of dose range-finding studies, groups of Fischer 344 rats were administered 1,4-dichlorobenzene at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks (NTP 1987). At sacrifice, animals were examined grossly and major tissues were examined histologically. No compound-related cardiovascular effects were observed at any dose level. In parallel studies, $B6C3F_1$ mice were administered 1,4-dichlorobenzene at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks. As with the rats, no compound-related cardiovascular effects were observed in mice at any of the doses used (NTP 1987).

In 2-year exposure studies in Fischer 344 rats, no cardiovascular effects were reported in males or females that received 1,4-Dichlorobenzene by gavage in corn oil at levels up to 300 or 600 mg/kg/day, respectively (NTP 1987). In similarly dosed $B6C3F_1$ mice, no cardiovascular effects were reported in either sex at doses up to 600 mg/kg/day (NTP 1987).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to 1,4-dichlorobenzene.

In a series of dose range-finding studies, groups of Fischer 344 rats were administered 1,4-dichlorobenzene at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks (NTP 1987). At sacrifice, animals were examined grossly and major tissues were examined histologically. Gastrointestinal effects were observed at doses of 1,200 mg/kg/day or more and consisted of epithelial necrosis and villar bridging of the mucosa of the small intestines. No gastrointestinal effects were noted in rats treated with 1,4-dichlorobenzene at doses of 900 mg/kg/day or less (NTP 1987). In parallel studies with $B6C3F_1$ mice, no compound-related gastrointestinal effects were observed after administration of 1,4-dichlorobenzene at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks (NTP 1987).

In 2-year exposure studies in Fischer 344 rats, no gastrointestinal effects were reported in males or females that received 1,4-dichlorobenzene by gavage in corn oil at levels up to 300 or 600 mg/kg/day, respectively

(NTP 1987). In similarly dosed B6C3F$_1$ mice, no gastrointestinal effects were reported in either sex at doses up to 600 mg/kg/day (NTP 1987).

Hematological Effects. A 21-year-old pregnant woman who had eaten l-2 blocks of 1,4-dichlorobenzene toilet air freshener per week throughout pregnancy developed severe microcytic, hypochromic anemia with excessive polychromasia and marginal nuclear hypersegmentation of the neutrophils. Heinz bodies were seen in a small number of the red cells. After she discontinued this practice (at about 38 weeks of gestation), her hemoglobin levels began to rise steadily. She gave birth to a normal infant with no hematological problems, and her own red blood cells were again normal at the final check 6 weeks after delivery (Campbell and Davidson 1970). Acute hemolytic anemia and were reported to have occurred in a 3-year-old boy who had played with 1,4-dichlorobenzene crystals (Hallowell 1959). It is not clear whether this child had actually ingested any of the 1,4-dichlorobenzene crystals.

Hematological effects reported in animal studies mainly concern effects on red cells in rats and on white cells in mice. Groups of male Fischer 344 rats (Ln=1/group) were administered 13-2,790 mg/kg body weight of 1,4-dichlorobenzene once via corn oil gavage. Twenty-four hours after dosing, the animals were weighed and exsanguinated. No hematological alterations were noted in any of the treated rats (Allis et al. 1992).

No adverse effects on hemoglobin levels or hematocrit were seen in adult male albino rats dosed with 1,4-dichlorobenzene by gavage in corn oil at levels up to 40 mg/kg/day for 90 days (Carlson and Tardiff 1976).

In Fischer 344 rats administered 1,4-dichlorobenzene by gavage in corn oil, 7 days a week for 13 weeks at doses of 75-600 mg/kg/day, no compound-related hematological effects were noted (Bornhard et al. 1988). In a series of experiments performed by Hollingsworth et al. (1956), male rats were administered 1,4-dichlorobenzene by gavage in olive oil at doses of 10-500 mg/kg/day, 5 days a week for 4 weeks; female rats received 1,4-dichlorobenzene in like manner at doses of 18.8-376 mg/kg/day, 5 days a week for 192 days; and male and female rabbits received 500 mg/kg/day 1,4-dichlorobenzene, 5 days per week for 367 days. Administration of 1,4-dichlorobenzene produced no hematological effects at any dose.

In another 13-week study in Fischer 344 rats, male rats that received 1,4-dichlorobenzene at 300 mg/kg/day and above had decreased hematocrit levels, red blood cell counts, and hemoglobin concentrations (NTP 1987). None of these hematologic effects were consistently seen in female rats at the same dosage level; however, a decrease in mean corpuscular volume was noted in females at doses of 600 mg/kg/day or more. In a parallel study in male and female $B6C3F_1$ mice dosed with 84.4-900 mg/kg/day 1,4-dichlorobenzene for 13 weeks, no hematological effects were noted in male or female mice at doses up to 900 mg/kg/day (NTP 1987); however, in another study $B6C3F_1$ mice dosed with 600-1,800 mg/kg/day 1,4-dichlorobenzene for 13 weeks, showed hematologic effects including 34-50% reductions in the white cell counts in all male dose groups; these decreases were accompanied by 26-33% decreases in lymphocytes and 69-82% decreases in neutrophils. No hematological effects were noted in female $B6C3F_1$ mice at doses up to 1,800 mg/kg/day (NTP 1987).

No hematologic effects were reported in 2-year studies in which male Fischer 344 rats received 1,4-dichlorobenzene at levels up to 300 mg/kg/day/day and female rats received levels up to 600 mg/kg/day (NTP 1987). Similar results were reported in $B6C3F_1$ mice of both sexes exposed to 600 mg/kg/day 1,4-Dichlorobenzene for 2 years (NTP 1987).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,4-dichlorobenzene.

In a series of dose range-finding studies, groups of Fischer 344 rats were administered 1,4-dichlorobenzene at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks. At sacrifice, animals were examined grossly and major tissues were examined histologically. No musculoskeletal effects were noted in any of the 1,4-dichlorobenzene-treated rats. In parallel studies with $B6C3F_1$ mice, no compound-related musculoskeletal effects were observed after administration of 1,4-dichlorobenzene at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks (NTP 1987).

In 2-year exposure studies in Fischer 344 rats, no musculoskeletal effects were reported in males or females that received 1,4-dichlorobenzene by gavage in corn oil at levels up to 300 or 600 mg/kg/day, respectively. In similarly dosed $B6C3F_1$ mice, no musculoskeletal effects were reported in either sex at doses up to 600 mg/kg/day (NTP 1987).

Hepatic Effects. A single case study was located regarding hepatic effects in humans after oral exposure to 1,4-dichlorobenzene. In this case report, the author describes a 3-year-old boy who had been playing with crystals containing 1,4-dichlorobenzene for 4-5 days before being admitted to the hospital. On admission, the boy was jaundiced and his mucous membranes were pale. After a blood transfusion, the child gradually improved. It was unclear whether the boy actually ingested any of the 1,4-dichlorobenzene (Hallowell 1959).

The acute hepatotoxicity and response of hepatic cytochrome P-450 in response to dosing with 1,4-dichlorobenzene were evaluated in groups of male Fischer 344 rats (n=1/group) given one dose of 13-2,790 mg/kg body weight by corn oil gavage. Twenty-four hours after dosing, the animals were weighed and sacrificed. Serum was collected and analyzed for total bilirubin, cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase. The liver was weighed and slices examined histopathologically. Liver microsomes were prepared and assayed for P-450, in addition to liver protein determinations. 1,4-Dichlorobenzene did not produce liver necrosis at any dose. There was also no effect observed on serum levels of ALT and AST. Hepatic cytochrome P-450 levels were increased about 30% by 1,4-dichlorobenzene beginning at 380 mg/kg and remaining elevated at all higher doses. No consistent pattern of change was found for indicators of hepatobiliary damage, serum cholesterol, serum alkaline phosphatase, and total bilirubin (Allis et al. 1992).

The effects of 1,4-dichlorobenzene were compared in male F344 rats given 0 (corn oil control), 25, 75, 150, and 300 mg/kg/day 1,4-dichlorobenzene (n=6-8/group/time) by daily oral gavage 5 days per week for 1 week. Replicative DNA synthesis was studied using subcutaneously implanted osmotic pumps containing 5-bromo-2'-deoxyuridine (BrdU) to determine the hepatocyte labeling index. Livers were removed, weighed, and then immunostained. Morphological examination of the liver sections from all lobes was performed from control and 300 mg/kg group rats. 1,4-Dichlorobenzene treatment for 1 week did not produce morphological changes in the rat livers. 1,4-Dichlorobenzene produced significant dose-related increases in relative liver weight in the rats, which were also associated with mild centrilobular hypertrophy. At 300 mg/kg, relative liver weight was significantly increased. Significant dose-related increases in microsomal cytochrome P-450 content were observed in rats given 150 and 300 mg/kg 1,4-dichlorobenzene for 1 week, with a significant dose-related induction of microsomal 7-pentoxyresorufin O-depentylase activity observed in rats given 75-300 mg/kg 1,4-dichlorobenzene. The hepatocyte labeling

index values were only increased in animals given 300 mg/kg 1,4-dichlorobenzene (225% of controls) (Lake et al. 1997).

In a series of experiments, Eldridge et al. (1992) studied the acute hepatotoxic effects of 1,4-dichlorobenzene and the role of cell proliferation in hepatotoxicity in B6C3F$_1$ mice and Fischer 344 rats. Mice and rats received a single dose of 1,4-dichlorobenzene by gavage in corn oil of 600, 900, or 1,200 mg/kg/day. At 1, 2, 4, and 8 days after 1,4-dichlorobenzene treatment, selected animals were injected intraperitoneally with 5-bromo-2'-deoxyuridine (BrdU) 2 hours prior to sacrifice to monitor cell proliferation. Other groups of mice and rats were sacrificed 24 or 48 hours after dosing, blood was collected for liver enzyme analysis, and liver sections were collected for histopathology. In mice dosed with 600 mg/kg/day 1,4-dichlorobenzene, liver weights were significantly increased 48 hours after dosing. Labeling index (LI), indicative of cell proliferation, peaked 24 hours after dosing in females and 48 hours in males. Activities of serum enzymes associated with liver damage (alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, sorbitol dehydrogenase) were not affected by 1,4-dichlorobenzene. Twenty-four and 48 hours after administration of 1,4-dichlorobenzene, the livers of males showed periportal hepatocytes with vacuolated cytoplasm and centrilobular hepatocytes with granulated basophilic cytoplasm; the severity of these changes was dose-related at 48 hours, but not at 24 hours. Similar but less pronounced effects were seen in females at 24 hours. In rats, liver weights were significantly increased at all time points after administration of 600 mg/kg/day 1,4-dichlorobenzene. The LI peaked 24 hours after dosing and was still elevated after 48 hours. Necrosis was not observed in the livers of mice or rats after treatment with 1,4-dichlorobenzene.

In pregnant CD rats administered 1,4-dichlorobenzene in corn oil at doses of 250-1,000 mg/kg/day on Gd 6-15, no differences in maternal liver weight were noted (Giavini et al. 1986); however, hepatic effects have been reported in other oral studies in which 1,4-dichlorobenzene has been administered to test animals by gavage (discussed below). These effects have ranged from temporary elevation of hepatic enzymes to hepatic degeneration and necrosis.

The effects of 1,4-dichlorobenzene were compared in male B6C3F$_1$ mice given 0 (corn oil control), 300, and 600 mg/kg/day 1,4-dichlorobenzene (n=6-8/group/time) by daily oral gavage 5 days per week for 1 week. Replicative DNA synthesis was studied using subcutaneously implanted osmotic pumps containing BrdU to assess the hepatocyte labeling index. Livers were removed, weighed, and immunostained.

Morphological examination of the liver sections was performed for control and 600 mg/kg groups. Biochemical analysis of liver whole homogenates was performed. 1,4-Dichlorobenzene produced significant dose-related increases in relative liver weight, which were associated with marked centrilobular hypertrophy. Relative liver weights were increased for mice in both the 300 and 600 mg/kg groups at all time points, with minimal centrilobular hypertrophy observed in 600 mg/kg group mice. No other histological abnormalities were observed in the liver sections. Administration of 1,4-dichlorobenzene also produced a sustained induction of microsomal cytochrome P-450 content and 7-pentoxyresorufin O-dependentylase activity. Significant dose-related induction of microsomal cytochrome P-450 content was induced in mice given 600 but not 300 mg/kg 1,4-dichlorobenzene. Microsomal 7-pentoxyresorufin O-dependentylase activity was significantly induced in mouse liver microsomes at doses of 300 and 600 mg/kg 1,4-dichlorobenzene. Western immunoblotting studies demonstrated that 1,4-dichlorobenzene induced CYP2B isoenzyme(s) in mouse liver microsomes at 300 and 600 mg/kg 1,4-dichlorobenzene. The hepatocyte labeling index values were also significantly increased in mice given 300 and 600 mg/kg 1,4-dichlorobenzene (Lake et al. 1997).

In male $B6C3F_1$ mice, single doses of 600, 1,000 or 1,800 mg/kg/day 1,4-dichlorobenzene administered by gavage in corn oil resulted in significantly elevated BrdU labeling of hepatocytes at the 1,000 and 1,800 mg/kg/day doses. In addition, single doses of 1,800 mg/kg resulted in a 4.5fold increase in serum alanine aminotransferase (ALT) activity and severe centrilobular hepatocyte swelling. In a companion time-course study, single doses of 1,800 mg/kg 1,4-dichlorobenzene administered by gavage in corn oil resulted in significantly elevated BrdU labeling in hepatic samples on days 2, 3, and 4, but not days 1 or 7. ALT activity was significantly elevated in 1,4-dichlorobenzene-treated mice on day 2 only. In all other aspects, hepatic toxicity was not evident in mice dosed with 1,800 mg/kg 1,4-dichlorobenzene (Umemura et al. 1996).

1,4-Dichlorobenzene has been shown to produce disturbances in porphyrin metabolism after high-level/ acute-duration exposure. Increased excretion of porphyrins, especially coproporphyrin and uroporphyrin, are considered to be indicators of liver damage. Administration of 1,4-dichlorobenzene in liquid paraffin to male rats at gradually increasing doses, until a dose level of 770 mg/kg/day was maintained for 5 days, resulted in high porphyrin excretion (Rimington and Ziegler 1963). Mean peak values of urinary coproporphyrin increased to about 10-15-fold above levels in controls. A 37-100-fold increase in urinary uroporphyrin levels occurred; porphobilinogen levels increased 200-530-fold; and a 10-fold increase in

δ-aminolevulinic acid (δ-ALA) levels was observed. In the liver itself, coproporphyrin levels were similar to controls, uroporphyrin levels were increased 46-fold, and protoporphyrin levels were increased 6-fold. These dramatic increases, which suggest severe damage to the liver, were not observed when 1,4-dichlorobenzene was administered to rats at higher levels (850 mg/kg/day) in 1% cellofas (Rimington and Ziegler 1963) or at lower levels for a longer period of time in another study (Carlson 1977), as discussed below. Also, Trieff et al. (1991) have used animal data on porphyrogenicity from various chlorinated benzenes to perform a QSAR study allowing prediction of ambient water criteria.

Changes in other markers of liver function including cytochrome P-450 levels, and activities of some drug-metabolizing enzymes (aminopyrine N-demethylase and aniline hydroxylase) were investigated in rats treated with of 1,4-dichlorobenzene by gavage at 250 mg/kg/day for up to 3 days (Ariyoshi et al. 1975). Activity of δ-ALA synthetase, an enzyme used in synthesis of the heme moiety found in cytochromes, was increased 42% by treatment with 1,4-dichlorobenzene. However, the cytochrome P-450 content did not change, although the microsomal protein content of liver preparations was increased. The toxicological significance of these findings is not clear since δ-ALA synthetase activity did not correlate with cytochrome P-450 concentration.

Effects on hepatic enzyme activities were reported to have occurred in adult male rats that were given 1,4-dichlorobenzene by gavage for 14 days (Carlson and Tardiff 1976). Significant decreases in hexobarbital sleeping time and a 6.5-fold increase in serum isocitrate dehydrogenase activity were observed after a 14-day treatment regimen at 650 mg/kg/day. In addition, even at considerably lower levels (20 or 40 mg/kg/day) increases were observed in the activities of hepatic microsomal xenobiotic metabolic systems including levels of glucuronyl transferase, and benzpyrene hydroxylase and O-ethyl-O-nitrophenyl phenylphosphorothionate (EPN) detoxification to nitrophenol. In a 90-day study at the same dosage levels, significant increases were seen in EPN detoxification, benzpyrene hydroxylase, and azoreductase levels. The former 2 levels were still elevated at 30 days after the cessation of administration of the compound. Most increases were noted at 20 mg/kg/day and above as in the 14-day studies; however, azoreductase levels were elevated even at 10 mg/kg/day (Carlson and Tardiff 1976). These observations are important because they demonstrate that hepatic effects occur at levels of 1,4-dichlorobenzene that are far below those associated with severe histopathology.

The effects of 1,4-dichlorobenzene were compared in male F344 rats given 0 (corn oil control), 25, 75, 150, and 300 mg/kg/day 1,4-Dichlorobenzene (n=6-8/group/time) by daily oral gavage 5 days per week for 4 and 13 weeks. Replicative DNA synthesis was studied using subcutaneously implanted osmotic pumps containing 5-bromo-2'-deoxyuridine (BrdU) during study weeks 3-4 and 12-13. Livers were removed, weighed, and then immunostained. Morphological examination of the liver sections was performed from control and 300 mg/kg group rats in the 13-week exposure group. 1,4-Dichlorobenzene treatment produced a mild centrilobular hypertrophy, seen in rats given 300 mg/kg 1,4-dichlorobenzene for 13 weeks. No other histological abnormalities were observed in the liver sections. 1,4-Dichlorobenzene produced significant dose-related increases in relative liver weight in the rats, which were associated with mild centrilobular hypertrophy. At 300 mg/kg, relative liver weight was significantly increased. Significant increases in relative liver weight were observed in rats given 75 and 150 mg/kg 1,4-dichlorobenzene for 4 weeks and 150 mg/kg 1,4-dichlorobenzene for 13 weeks. Administration of 1,4-dichlorobenzene also produced a sustained induction of microsomal cytochrome P-450 content and 7-pentoxyresorufin O-dependentylase activity. Significant dose-related increases in microsomal cytochrome P-450 content were observed in rats given 25-300 mg/kg 1,4-dichlorobenzene for 4 weeks and 75-300 mg/kg 1,4-dichlorobenzene for 13 weeks. A significant dose-related induction of microsomal 7-pentoxyresorufin O-dependentylase activity was observed in rats given 75-300 mg/kg 1,4-dichlorobenzene for 4 weeks and 25-300 mg/kg 1,4-dichlorobenzene for 13 weeks. Western immunoblotting studies demonstrated that 1,4-Dichlorobenzene induced CYP2B isoenzyme(s) in rat liver microsomes at 75 and 300 mg/kg 1,4-dichlorobenzene (Lake et al. 1997).

Histopathological effects in the liver, including cloudy swelling and centrilobular necrosis, were observed after gavage administration of 1,4-dichlorobenzene in rats (2 per group) at 500 mg/kg/day for 4 weeks; similar results (cloudy swelling, focal caseous necrosis) were obtained in rabbits (5 per group) given 92 doses of 1,000 mg/kg/day 1,4-dichlorobenzene in olive oil over a 219-day period (Hollingsworth et al. 1956). The interpretation of this study is limited by the size of the test groups and the fact that observations in controls were not presented. Histopathological changes were also reported in a 13-week study in which rats received 1,4-dichlorobenzene by gavage (NTP 1987). Doses of 1,200 or 1,500 mg/kg/day produced degeneration and necrosis of hepatocytes. Serum cholesterol levels were increased by doses of 600 mg/kg/day or more in male rats and by 900 mg/kg/day or more in female rats, while serum triglycerides and protein levels were reduced at doses of 300 mg/kg/day or more in male rats. Urinary porphyrins were increased in both sexes at 1,200 mg/kg/day or more. However, these increases

were modest and considered by the authors to indicate mild porphyrinuria rather than hepatic porphyria. Liver porphyrins were not increased at any dose. In a second 13-week study in the same laboratory, hepatic effects were not observed in rats at dosage levels up to 600 mg/kg/day (NTP 1987).

Similar hepatic effects were reported in two 13-week gavage studies in mice (NTP 1987). Hepatocellular degeneration was observed in both sexes at all doses (600-1,800 mg/kg/day). Serum cholesterol levels were increased in male mice at doses of 900 mg/kg/day or more, and serum protein and triglycerides were increased at doses of 1,500 mg/kg/day or more. These changes were thought by the authors to reflect the hepatic effects of this compound. Hepatic porphyria was not found in mice at any dose level in this study. Because hepatic effects were seen in mice in all dose groups in the first 13-week study, a second 13-week study was conducted at lower dosage levels. Hepatocellular cytomegaly was observed in mice at doses of 675 mg/kg/day and above. The lowest level at which hepatic effects were observed in mice was 600 mg/kg/day (in the first study).

Other intermediate-duration oral studies with 1,4-dichlorobenzene have reported liver toxicity. In female rats dosed with 1,4-dichlorobenzene by gavage for about 6 months, doses of 188 mg/kg/day and above resulted in increased liver weights. At 376 mg/kg/day, slight cirrhosis and focal necrosis of the liver were also observed (Hollingsworth et al. 1956). No effects on the liver were seen at a dose of 18.8 mg/kg/day. Based on a minimal LOAEL (increased liver weight) of 188 mg/kg/day, an intermediate-duration MRL of 0.4 mg/kg/day was calculated as described in the footnote to Table 2-2 and Appendix A (Hollingsworth et al. 1956).

The ability of 1,4-dichlorobenzene to induce porphyria was investigated in female rats that were administered 1,4-dichlorobenzene by gavage for up to 120 days (Carlson 1977). Slight but statistically significant increases in liver porphyrins were seen in all dosed rats (50-200 mg/kg/day) at 120 days. Urinary excretion of δ-ALA, porphobilinogen, or porphyrins was not increased over control levels. These results indicated that 1,4-dichlorobenzene had only a slight potential for causing porphyria at these doses in female rats compared with the far more pronounced porphyrinogenic effects reported earlier in male rats that received 770 mg/kg/day for 5 days in a study by Rimington and Ziegler (1963). However, sex-related differences in susceptibility to 1,4-dichlorobenzene's effects on these parameters cannot be ruled out in a comparison of these two studies.

The role of cell proliferation in liver toxicity induced by 1,4-dichlorobenzene was examined in groups of mice (5-7 per sex per dose level) administered 0 (vehicle only), 300, or 600 mg/kg 1,4-dichlorobenzene in corn oil by gavage 5 days a week for 13 weeks (Eldridge et al. 1992). The liver toxicity induced by 1,4-dichlorobenzene was also examined in groups of female rats (5-7 per dose level) administered 0 (vehicle only), or 600 mg/kg 1,4-dichlorobenzene in corn oil by gavage 5 days a week for 13 weeks. At various times during the study, mice were implanted with osmotic pumps to deliver BrdU. Liver weights were significantly increased in high-dose male and female mice and in female rats throughout the 13-week study. Treated male mice showed a centrilobular pattern of labeled hepatocytes, whereas females were labeled throughout the lobules. At the lower-dose level, liver weight was increased in male and female mice at weeks 6 and 13. In a group of mice in which treatment with 600 mg/kg/day ceased after 5 weeks and the animals were allowed to recover for 1 week, liver weight returned to control values. The authors concluded that 1,4-dichlorobenzene induced a mitogenic stimulation of cell proliferation in the liver rather than a regenerative response following cytotoxicity. This was evidenced by an increase in liver weight without increase in liver-associated plasma enzymes (Eldridge et al. 1992).

The effects of 1,4-dichlorobenzene were determined in male B6C3F_1 mice given 0 (corn oil control), 300, and 600 mg/kg/day 1,4-dichlorobenzene (n=6-8/group/time) by daily oral gavage 5 days per week for 4 and 13 weeks. Replicative DNA synthesis was studied using subcutaneously implanted osmotic pumps containing BrdU during study weeks 3-4 and 12-13. Livers were removed, weighed, and immunostained. Morphological examination of the livers was performed for control and 600 mg/kg group mice at 13 weeks. Biochemical analysis of liver whole homogenates was also performed. 1,4-Dichlorobenzene produced significant dose-related increases in relative liver weight in the mice, which were associated with marked centrilobular hypertrophy. Relative liver weights were increased for mice in both the 300 and 600 mg/kg groups at all time points. At 13 weeks, a marked centrilobular hypertrophy was observed in the 600 mg/kg group. No other histological abnormalities were observed in the liver. Administration of 1,4-dichlorobenzene also produced a sustained induction of microsomal cytochrome P-450 content and 7-pentoxyresorufin O-depentylase activity. Significant dose-related induction of microsomal cytochrome P-450 content was induced in mice given 600 but not 300 mg/kg 1,4-dichlorobenzene for treatments of 4 and 13 weeks. Microsomal 7-pentoxyresorufin O-depentylase activity was significantly induced in mouse liver microsomes at doses of 300 and 600 mg/kg 1,4-dichlorobenzene. Western immunoblotting studies demonstrated that 1,4-dichlorobenzene induced CYP2B isoenzyme(s) in mouse liver microsomes at 300 and 600 mg/kg 1,4-dichlorobenzene. Hepatocyte labeling index values were significantly increased in mice

given 300 and 600 mg/kg 1,4-dicholorobenzene for 4 weeks (420% and 395% of controls, respectively) (Lake et al. 1997).

Studies of the hepatic effects of chronic 1,4-dichlorobenzene exposure are sparse. The toxicity of 1,4-dichlorobenzene was evaluated in a group of 7 rabbits administered 1,4-dichlorobenzene in olive oil at a dose of 500 mg/kg/day a total of 263 times over a 367-day period. Slight changes in the liver (cloudy swelling and a few areas of focal caseous necrosis) were noted at sacrifice (Hollingsworth et al. 1956).

In the only study of lifetime oral exposure to 1,4-dichlorobenzene in laboratory animals, groups of male and female Fischer 344 rats were administered 1,4-dichlorobenzene by gavage in corn oil 5 days a week for 103 weeks at doses of 150 or 300 mg/kg/day (males) or 300 or 600 mg/kg/day (females). Groups of male and female B6C3F_1 mice were administered 1,4-dichlorobenzene at doses of 300 or 600 mg/kg/day by gavage in corn oil, 5 days a week for 103 weeks. No hepatic effects were seen in rats; in mice, the incidence of hepatocellular degeneration was greatly increased in treated mice (in males: 0 of 50 control, 36 of 49 low-dose, 39 of 50 high-dose; in females 0 of 50 control, 8 of 48 low-dose, 36 of 50 high-dose). The primary degenerative change was cellular swelling with clearing or vacuolation of the cytoplasm. Individual hepatocytes had pyknotic or karyorrhectic nuclei and condensed eosinic cytoplasm. Some necrotic hepatocytes formed globular eosinophilic masses in the sinusoids (NTP 1987).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to 1,4-dichlorobenzene.

The role of cell proliferation in kidney toxicity induced by 1,4-dichlorobenzene was examined in groups of male and female B6C3F_1 mice and Fischer 344 rats (Umemura et al. 1992). Mice were administered 300 or 600 mg/kg 1,4-dichlorobenzene; in rats, males received 150 or 300 mg/kg 1,4-dichlorobenzene while females received 300 or 600 mg/kg 1,4-dichlorobenzene. All doses were administered by gavage in corn oil for 4 consecutive days. Cell proliferation was evaluated by means of immunohistochemical measurement of BrdU-labeled cells. In mice, kidney weights and cell proliferation in the kidney tubules were not altered by 1,4-dichlorobenzene treatment; in rats, kidney weight was significantly increased in male rats at both dose levels, but was not affected in females. Cell proliferation was greatly increased in the proximal convoluted tubule from high-dose males. A lesser increase was seen in the proximal straight

tubule from high-dose males; no increase was observed in the distal tubule from males or in any kidney region from treated female rats.

The effects of 1,4-dichlorobenzene were compared in male F344 rats given 0 (corn oil control), 25, 75, 150, and 300 mg/kg/day 1,4-dichlorobenzene (n=6-8/group/time) and male B6C3F_1 mice given 0 (corn oil control), 300, and 600 mg/kg/day 1,4-dichlorobenzene (n=6-8/group/time) by daily oral gavage 5 days per week for 1 week. Replicative DNA synthesis was studied using subcutaneously implanted osmotic pumps containing 5-bromo-2'-deoxyuridine during study weeks 0-l, 3-4, and 12-13. After sacrifice, the kidneys were removed, weighed, and immunostained. In rats, significant increases in relative kidney weight were observed in those rats administered 150 and 300 mg/kg 1,4-dichlorobenzene for 4 and 13 weeks. 1,4-Dichlorobenzene treatment produced significant increases in rat renal P1/P2 proximal tubule cell labeling index values at all time points. Significant increases were seen in the following groups: 75 mg/kg 1,4-dichlorobenzene at 4 weeks (250% of controls); 150 mg/kg 1,4-dichlorobenzene at 4 and 13 weeks (400% and 440% of controls, respectively); and 300 mg/kg 1,4-dichlorobenzene at 1, 4, and 13 weeks (170%, 475%, and 775% of controls, respectively). A significant increase in rat P3 renal proximal tubule cell labeling index values was observed in 300 mg/kg 1,4-dichlorobenzene group rats at weeks 4 (185% of controls) and 13 (485% of controls). In contrast, some reduction in rat P3 renal proximal tubule cell labeling index values was observed in 75-300 mg/kg 1,4-dichlorobenzene group rats at 1 week. In contrast, 1,4-dichlorobenzene treatment produced little effect on mouse renal P1/P2 proximal tubule cell labeling index values at all time points tested. No significant increase was seen in 300 or 600 mg/kg 1,4-dichlorobenzene groups for 1 and 13 weeks, but significant increases were seen at 4 weeks (205% and 170% of controls, respectively). Neither 300 nor 600 mg/kg 1,4-dichlorobenzene for 1,4, or 13 weeks had much effect on mouse P3 renal proximal tubule cell labeling index values (Lake et al. 1997).

In a study which examined the role of the protein $\alpha_{2\mu}$-globulin in 1,4-dichlorobenzene-induced nephrotoxicity in male rats, NCI-Black-Reiter (NBR) rats, known not to synthesize the hepatic form of the $\alpha_{2\mu}$-globulin, were administered 500 mg/kg/day 1,4-dichlorobenzene by gavage in corn oil for 4 consecutive days. Positive controls consisted of Fischer 344 male rats treated with lindane; the results were also compared with those obtained in a group of female Fischer 344 rats treated with lindane. End points examined consisted of kidney lesions and protein droplet evaluation. $\alpha_{2\mu}$-Globulin was detected in kidney sections from male Fischer 344 rats, but not in male NBR or female Fischer 344 rats. No lesions or

hyaline droplets were detected in treated or control male NBR and female Fischer 344 rats (Dietrich and Swenberg 1991).

Renal tubular degeneration has been observed in male but not female Fischer 344 rats in two 13-week gavage studies (NTP 1987). These effects were severe in male rats receiving 300 mg/kg/day or more in the first study, but in the second study, only slight changes were seen at 300 mg/kg/day, while moderate tubular degeneration was present at 600 mg/kg/day. Renal effects reported in another intermediate-duration gavage study in rats included increased renal weights at doses of 188 mg/kg/day or more (Hollingsworth et al. 1956). Renal effects were not observed in mice in either of two 13-week gavage studies using dosage regimens of 600-1,800 mg/kg/day and 84.4-900 mg/kg/day (NTP 1987).

In a study designed to investigate the mechanism of renal toxicity for 1,4-dichlorobenzene reported in the NTP (1987) studies, 1,4-dichlorobenzene administered by gavage to male Fischer 344 rats at 7 daily doses of 120 or 300 mg/kg/day significantly increased the level of protein droplet formation in the kidneys of males but not females (Charbonneau et al. 1987). Administration of a single dose of ^{14}C-1,4-dichlorobenzene by gavage at 500 mg/kg gave similar results. An analysis of the renal tissue of animals administered radio-labeled 1,4-dichlorobenzene indicated that it was reversibly associated with the protein $\alpha_{2\mu}$-globulin. In a study designed to correspond to the experimental conditions of the 13-week NTP (1987) study in rats, 1,4-dichlorobenzene was administered to Fischer 344 rats by gavage at 75-600 mg/kg/day for 13 weeks; interim sacrifices were performed at 4 weeks (Bomhard et al. 1988). At 4 weeks, females had no structural damage to the kidneys, while males experienced damage at the corticomedullary junction at a doses of 150 mg/kg or more; damage consisted of dilated tubules with granular and crystalline structures, hyaline droplets, and desquamated epithelia. At all dose levels in the males, hyaline bodies were seen in the proximal tubule epithelial cells. At 13 weeks, males exhibited an increase urinary excretion of lactate dehydrogenase (LDH) and of epithelial cells over the entire dose range tested. These changes did not always appear to be dose-related. No signs of structural damage were seen in the females' kidneys. In males, a dose-dependent incidence of hyaline droplets in the cortical tubular epkhelium was seen at 75 mg/kg/day and above. At ≥150 mg/kg/day, single-cell necrosis was observed, and at 300 and 600 mg/kg/day, epithelial desquamation of longer parts of the tubules were occasionally seen.

In the only available study of chronic-duration oral exposure to 1,4-dichlorobenzene, renal effects were observed to occur preferentially in males. Male Fischer 344 rats exposed to 1,4-dichlorobenzene at

150 and 300 mg/kg/day by gavage for 2 years exhibited the following effects with greater severity and in greater numbers: nephropathy, epithelial hyperplasia of the renal pelvis, mineralization of the collecting tubules in the renal medulla, and focal hyperplasia of renal tubular epithelium (NTP 1987). There was also increased incidence of nephropathy in female rats dosed with 1,4-dichlorobenzene at 300 and 600 mg/kg/day, but there was minimal hyperplasia of the renal pelvis or tubules. Two-year administration of 1,4-dichlorobenzene at 300 and 600 mg/kg/day also increased the incidence of nephropathy in male $B6C3F_1$ mice. Renal tubular degeneration was noted in female mice but these changes occurred at a lower frequency and were qualitatively different from those in male rats (NTP 1987).

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to 1,4-dichlorobenzene.

In a series of dose range-finding studies, groups of Fischer 344 rats were administered 1,4-dichlorobenzene at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks. At sacrifice, animals were examined grossly and major tissues were examined histologically. No endocrine organs were affected in any of the 1,4-dichlorobenzene-treated rats. In parallel studies with $B6C3F_1$ mice, no compound-related endocrine effects were observed after administration of 1,4-dichlorobenzene at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks (NTP 1987).

In the only study of lifetime oral exposure to 1,4-dichlorobenzene in laboratory animals (NTP 1987), groups of male and female Fischer 344 rats were administered 1,4-dichlorobenzene by gavage in corn oil, 5 days a week for 103 weeks at doses of 150 or 300 mg/kg/day (males) or 300 or 600 mg/kg/day (females). Groups of male and female $B6C3F_1$ mice were administered 1,4-dichlorobenzene at doses of 300 or 600 mg/kg/day by gavage in corn oil, 5 days a week for 103 weeks. In the Fischer 344 rats, an increased incidence of parathyroid hyperplasia was observed in males (4 of 42 controls, 13 of 42 low-dose, 20 of 38 high-dose), while no effect was seen in females. In mice, the incidence of thyroid follicular cell hyperplasia increased with dose in males (1 of 47 control, 4 of 48 low-dose, 10 of 47 high-dose), but not in females. The incidence of adrenal medullary hyperplasia and focal hyperplasia of the adrenal gland capsule also increased with dose in males (controls, 11 of 47; low-dose, 21 of 48; high-dose, 28 of 49).

Dermal Effects. A 19-year-old black woman who had been eating 4-5 moth pellets made of 1,4-dichlorobenzene daily for 2.5 years developed symmetrical, well demarcated areas of increased pigmentation in a bizarre configuration over various parts of her body. After she discontinued this practice, the skin discolorations gradually disappeared over the next 4 months (Frank and Cohen 1961).

In laboratory animals, groups of Fischer 344 rats were administered 1,4-dichlorobenzene at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks. No dermal effects were noted in any of the 1,4-dichlorobenzene-treated rats. In parallel studies with $B6C3F_1$ mice, no compound-related dermal effects were observed after administration of 1,4-dichlorobenzene at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks (NTP 1987).

In the only study of lifetime oral exposure to 1,4-dichlorobenzene in laboratory animals (NTP 1987), groups of male and female Fischer 344 rats were administered 1,4-dichlorobenzene by gavage in corn oil, 5 days a week for 103 weeks at doses of 150 or 300 mg/kg/day (males) or 300 or 600 mg/kg/day (females). Groups of male and female $B6C3F_1$ mice were administered 1,4-dichlorobenzene at doses of 300 or 600 mg/kg/day by gavage in corn oil, 5 days a week for 103 weeks. No dermal effects have been reported in rats or mice at any of the studied doses.

Ocular Effects. No studies were located regarding the ocular effects in humans after oral exposure to 1,4-dichlorobenzene.

In a series of intermediate-duration studies, groups of Fischer 344 rats were administered 1,4-dichlorobenzene at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks. Ocular discharge was noted prior to death in males dosed with 1,200 mg/kg and in all rats exposed to 1,500 mg/kg. In parallel studies with $B6C3F_1$ mice, no compound-related ocular effects were observed after administration of 1,4-dichlorobenzene at concentrations ranging from 84.4 to 1,800 mg/kg/day by gavage in corn oil 5 days a week for 13 weeks (NTP 1987).

The ocular effects of oral administration of 1,4-dichlorobenzene were examined in groups of white (strain no reported) female rats and male and female rabbits. Rats received 1,4-Dichlorobenzene in olive oil at doses of 18.8-376 mg/kg/day, 5 days a week for 192 days; rabbits received 1,4-dichlorobenzene in olive oil

at a dose of 1,000 mg/kg/day for 219 days. Under the study conditions, administration of 1,4-dichlorobenzene did not produce cataracts in either species (Hollingsworth et al. 1956).

In chronic-duration toxicity studies in laboratory animals, Hollingsworth et al. (1956) found no evidence of cataract formation in rabbits administered a total of 263 doses of 500 mg/kg/day 1,4-Dichlorobenzene in olive oil over a 367-day period.

In two lifetime oral exposure studies (NTP 1987), groups of male and female Fischer 344 rats were administered 1,4-dichlorobenzene by gavage in corn oil, 5 days a week for 103 weeks at doses of 150 or 300 mg/kg/day (males) or 300 or 600 mg/kg/day (females); groups of male and female B6C3F $_1$ mice were administered 1,4-dichlorobenzene at doses of 300 or 600 mg/kg/day by gavage in corn oil, 5 days a week for 103 weeks. In both species, no ocular effects were noted at any of the studied doses.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to 1,4-dichlorobenzene.

The effects of acute exposure to 1,4-dichlorobenzene on body weight were examined in female Wistar rats given 1,4-dichlorobenzene suspended in 2% tragacanth gum solution (a suspending agent obtained from the dried gummy exudation of *Astragalus gummifer)* at a dose of 250 mg/kglday for 3 days. Under these conditions, no effects on body weight were seen (Ariyoshi et al. 1975). Male and female mice and female rats dosed once with 600 mg/kg/day 1,4-dichlorobenzene also showed no discernible changes in body weight (Eldridge et al. 1992). Male rats administered 770 mg/kg/day of 1,4-dichlorobenzene once a day for 5 days showed no changes in body weight (Rimington and Ziegler 1963). Pregnant CD rats that were administered 250-l ,000 mg/kg/day 1,4-dichlorobenzene in corn oil on Gd 6-15 experienced a reversible loss in maternal body weight (Giavini et al. 1986).

Body weight changes were observed in three studies in rats and mice (NTP 1987). In the first, both sexes of mice and female rats dosed at concentrations up to 1,000 mg/kg/day for 14 days by gavage demonstrated no changes in body weight during the test period. Male rats dosed at 500 mg/kg/day also showed no changes in body weight; however, a 7-12% decrease in body weight was noted in the 1,000 mg/kg/day dose group. In the second study (same route and duration as the first), male mice experienced a 13.3% decrease in body weight at the 250 mg/kg/day dose and a 14.7% decrease in body weight at the 2,000 mg/kg/day

dose; however, results of intermediate doses demonstrated that there was no observable dose-response relationship for body weight changes. Neither male nor female rats dosed with 500 mg/kg/day showed any effects on body weights; however, a dose of 1,000 mg/kg/day resulted in a 13.5% decrease in weight for males and a 16.7% decrease in females. In the third study, male rats gavaged with 0, 25, 75, or 150 mg/kg of 1,4-dichlorobenzene in corn oil for 7 days showed no changes in body weight; however, rats dosed at 300 mg/kg showed an approximately 10% decrease in body weight gain (Lake et al. 1997). The same study in male mice dosed with 0, 300, or 600 mg/kg of 1,4-dichlorobenzene in corn oil for 7 days showed no changes in body weight at any dose level (Lake et al. 1997).

In intermediate-duration studies, no compound-related effects on weight gain were noted in albino or Fischer 344 rats administered 1,4-dichlorobenzene by gavage in corn oil at doses up to 600 mg/kg/day, 7 days a week for 13 weeks (Bomhard et al. 1988; Carlson and Tardiff 1976). Male rats gavaged with 0 or 25 mg/kg of 1,4-dichlorobenzene in corn oil for 7 days showed no changes in body weight; however, rats dosed at 75, 150, or 300 mg/kg showed an approximately 10% decrease in body weight gain (Lake et al. 1997). The same study in male mice dosed with 0, 300, or 600 mg/kg of 1,4-dichlorobenzene in corn oil for 7 days showed no changes in body weight at any dose level (Lake et al. 1997). Male and female mice and female rats dosed with concentrations of 600 mg/kg/day 1,4-dichlorobenzene 5 days a week for 13 weeks also showed no discernible changes in body weight (Eldridge et al. 1992). In a series of dose range-finding studies, groups of Fischer 344 rats were administered 1,4-dichlorobenzene at concentrations ranging from 37.5 to 1,500 mg/kg/day by gavage in corn oil, 5 days a week for 13 weeks (NTP 1987). In the first of these studies, there were no treatment-related effects on body weight at doses up to 600 mg/kg/day. In the second study, final body weight was decreased by 11% in low-dose males (300 mg/kg/day) relative to controls; in high-dose males (1,500 mg/kg/day) the reduction was 32%. The effect was less marked in females (6% reduction at 900 mg/kg/day; 11% reduction at 1,200). In parallel studies with $B6C3F_1$ mice, no compound-related effects on body weight were observed after administration of 1,4-dichlorobenzene at concentrations up to 900 mg/kg/day; however, in the second study, final body weight was reduced in all males receiving 1,4-dichlorobenzene (11.4% at 1,500 mg/kg/day to 13.9% at 600 mg/kg/day) and in females at 600 mg/kg/day (10.3%) (NTP 1987).

In 2 lifetime oral exposure studies , groups of male and female Fischer 344 rats and $B6C3F_1$ mice were administered 1,4-dichlorobenzene by gavage in corn oil, 5 days a week for 103 weeks. Fischer 344 rats were administered 1,4-dichlorobenzene at doses of 150 or 300 mg/kg/day (males) or 300 or 600 mg/kg/day

(females); mice were administered 1,4-dichlorobenzene at doses of 300 or 600 mg/kg/day (NTP 1987). In mice, no effects on body weight attributable to treatment with 1,4-dichlorobenzene were observed at doses up to 600 mg/kg/day. In rats, body weight gain was depressed by 12.5% in high-dose males (300 mg/kg/day) and by 12.4% in high-dose females (600 mg/kg/day) relative to vehicle controls.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to 1,4-dichlorobenzene. Symmetrical lesions with a bizarre pattern of skin pigmentation over most of her body were reported in the case study of a 19-year-old black woman who ingested 4-5 moth pellets of 1,4-dichlorobenzene per day for a 2.5year period (Frank and Cohen 1961). The lesion disappeared 4 months after cessation. The described lesions may have been the result an immunological response to 1,4-dichlorobenzene. However, this possibility was not addressed by the authors.

Groups of Fischer 344 rats were administered 1,4-Dichlorobenzene at concentrations ranging from 300 to 1,500 mg/kg/day by gavage in corn oil, 5 days a week for 13 weeks (NTP 1987). Treatment-related immunological and lymphoreticular effects noted in the study included hypoplasia of the bone marrow and lymphoid depletion of the spleen and thymus in males and females at doses of 1,200 mg/kg/day and above. In parallel studies with $B6C3F_1$ mice administered 1,4-dichlorobenzene at concentrations ranging from 300 to 1,500 mg/kg/day, lymphoid necrosis in the thymus, lymphoid depletion in the spleen, and hematopoietic hypoplasia of the spleen and bone marrow were noted in both males and females at doses of 1,500 mg/kg/day and above (NTP 1987).

Minimal lymphoreticular changes were noted in a chronic-duration study (NTP 1987). Male rats administered doses of 150 or 300 mg/kg/day and female rats given 300 or 600 mg/kg/day of 1,4-dichlorobenzene by gavage 5 days a week for 2 years showed no discernible changes in the lymphoreticular system; however, mice dosed in a similar fashion and at a dose of 600 mg/kg/day showed an increased incidence of lymph node hyperplasia.

2.2.2.4 Neurological Effects

Two case studies have reported neurological effects in humans exposed to 1,4-Dichlorobenzene via ingestion have been reported in two case studies. A 21-year-old pregnant woman developed pica (a craving for unnatural substances) for 1,4-dichlorobenzene toilet bowl deodorizer blocks, which she consumed at the rate of l-2 per week throughout pregnancy (Campbell and Davidson 1970). Reported neurological effects included fatigue, dizziness, and mild anorexia. These effects, however, are common general symptoms that occur in many women during normal pregnancy. A 19-year-old black woman who ingested 4-5 pellets of 1,4-dichlorobenzene daily for about 2.5 years developed tremors and unsteadiness after she stopped eating this chemical. However, in the opinion of the neurologist who evaluated the woman in this case report, the effects were considered to be psychological rather than the physiological effects of withdrawal from 1,4-dichlorobenzene (Frank and Cohen 1961).

Two studies in laboratory animals indicate that oral exposure to 1,4-dichlorobenzene may result in adverse neurological effects. In a study performed by Rimington and Ziegler (1963), three male albino rats were administered daily doses of 1,4-dichlorobenzene in liquid paraffin at gradually increasing doses until a dose was reached (770 mg/kg/day) which resulted in high porphyrin excretion with very few fatalities; this dose was given for 5 days. Clinical symptoms associated with highly porphyric rats included extreme weakness, ataxia, clonic contractions, and slight tremors (a rarity). One rat receiving 1,4-dichlorobenzene developed left-sided hemiparesis. In Fischer 344 rats administered 1,4-dichlorobenzene by gavage in corn oil 5 days a week for 13 weeks, tremors and poor motor response were observed in males at 1,200 mg/kg/day and above, and in both sexes at 1,500 mg/kg/day. However, administration of 1,4-dichlorobenzene had no effect on brain weight or on the microscopical appearance of the brain, sciatic nerve, or spinal cord (NTP 1987).

In a chronic-duration study (NTP 1987), no neurological effects were noted either in rats dosed with 300 mg/kg/day of 1,4-dichlorobenzene, 5 days a week for 2 years, or in mice dosed with 600 mg/kg/day, 5 days a week for 2 years.

2.2.2.5 Reproductive Effects

Several studies were located which addressed the reproductive effects of oral exposure to 1,4-dichlorobenzene in laboratory animals.

In pregnant CD rats administered 1,4-dichlorobenzene by gavage in corn oil on Gd 6-15, doses up to 1,000 mg/kg/day had no adverse effect on the mean number of corpora lutea, mean number of implantations, mean percentage of pre- or post-implantation losses, or mean percentage of dams with resorptions (Giavini et al. 1986). In addition, male and female $B6C3F_1$ mice exposed to 1,4-dichlorobenzene by gavage in corn oil at doses of 600, 900, 1,000, 1,500, or 1,800 mg/kg/day, 5 days a week for 13 weeks showed no compound-related effects in regarding organ weight changes (organ/brain) of the testes or uteri; however, relative ovarian weights were significantly increased in the 1,500 mg/kg/day group. The gross and histological appearance of the mammary glands, testes, ovaries, and uteri were not affected by treatment with 1,4-dichlorobenzene (NTP 1987).

In a chronic-duration study (NTP 1987) no effects were noted in the reproductive organs in either the rats dosed with 300 mg/kg/day of 1,4-dichlorobenzene, 5 days a week for 2 years, or in mice dosed with 600 mg/kglday, 5 days a week for 2 years.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to 1,4-dichlorobenzene.

A dose-related increase in the incidence of an extra rib was observed in the fetuses of pregnant CD rats administered 1,4-dichlorobenzene by gavage on Gd 6-15 at doses of 500, 750, and 1,000 mg/kg/day (Giavini et al. 1986). A reduction in fetal weight was observed at 1,000 mg/kg/day. The reduction in fetal weight was not considered to be a fetotoxic effect since it was associated with a decrease in maternal weight gain at the same dosage level. The structural anomaly observed in these fetuses was dose-dependant but was not considered to be an true adverse effect by the authors. However, these results raise the question of whether 1,4-dichlorobenzene ingested by the dams reached developing fetal tissue and elicited a developmental effect.

The NOAEL and LOAEL for this study are recorded in Table 2-2 and plotted in Figure 2-2

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to 1,4-dichlorobenzene.

Gavage administration of 1,4-dichlorobenzene to B6C3F_1 mice and Fischer 344 rats at single doses of 300-l ,000 mg/kg/day did not result in unscheduled deoxyribonucleic acid (DNA) synthesis in the mouse hepatocytes or in the renal tissue of the rats (Steinmetz and Spanggord 1987a, 1987b). However, 1,4-Dichlorobenzene at the highest level did induce an increase in DNA replication (S-phase of cell division) in the renal tissue of the male rats and in the hepatocytes of the male mice. Based on a comparison with historical controls, the authors concluded that levels of DNA replication were also significantly elevated in the hepatocytes of female mice.

No evidence of a clastogenic effect was found in mouse bone marrow erythroblasts after a single gavage administration of 1,4-dichlorobenzene at 2,500 mg/kg/day (Herbold 1986a). Similarly, no evidence of clastogenic effects were found in mouse bone erythroblasts after a single oral administration of 2,5-dichlorophenol (the major metabolite of 1,4-dichlorobenzene) at 1,500 mg/kg/day (Herbold 1986b). 2,5-Dichlorophenol with or without metabolic activation did not induce an increase in mutagenic response in the Chinese hamster ovary HGPRT forward mutation assay (Litton Bionetics 1986a). This compound was also inactive in the Balb/3T3 *in vitro* transformation assay (Litton Bionetics 1985).

Cytogenetic effects were not found in bone marrow cells from mice treated with 1,4-dichlorobenzene by gavage at levels up to 1,800 mg/kg/day in a 13-week study (NTP 1987). No increase in micronucleated cells occurred even at levels that were extremely toxic to the test animals, resulting in liver toxicity and decreased survival rates. As noted by the authors of that study, the observed carcinogenic activity of 1,4-dichlorobenzene cannot be adequately predicted on the basis of the available genotoxicity data; all of the available information strongly suggests that 1,4-dichlorobenzene acts as a tumor promoter rather than as a mutagen. Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to 1,4-dichlorobenzene.

1,4-Dichlorobenzene was found to be carcinogenic in $B6C3F_1$ mice and male (but not female) Fischer 344 rats exposed to 1,4-dichlorobenzene for 2 years in a carcinogenesis bioassay (NTP 1987). 1,4-Dichlorobenzene was administered by gavage to male rats at doses of 150 or 300 mg/kg/day and female rats at doses of 300 or 600 mg/kg/day. Significant dose-related increases in the incidence of renal tubular cell adenocarcinomas were reported in male rats (controls, 2%; low-dose, 6%; high-dose, 14%). Spontaneous tumors of this type are uncommon in male Fischer 344 rats; they have been diagnosed in only 4 of 1,098 (0.4%) of the corn oil-gavage controls in previous NTP studies. There were no tubular cell tumors in dosed or vehicle-control female rats. There also was a marginal increase in the incidence of mononuclea cell leukemia in dosed male rats which was only slightly higher than the incidence in historical controls from the same laboratory. The NTP study concluded that 1,4-Dichlorobenzene was carcinogenic in male rats, but not in female rats.

In a 2-year bioassay in $B6C3F_1$ mice that received 1,4-dichlorobenzene at 300 or 600 mg/kg/day (NTP 1987) increased incidences of hepatocellular carcinomas were observed in high-dose male mice (controls, 28%; low-dose, 22.5%; high-dose, 64%) and high-dose female mice (controls, 10%; low-dose, 10.4%; high-dose, 38%). Hepatocellular adenomas were increased in high- and low-dose male mice (controls, 10%; low-dose, 26.2%; high-dose, 32%) and in high-dose female mice (controls, 20%; low-dose, 12.5%; high-dose, 42%). Female control mice in this bioassay had a substantially higher incidence of liver tumors than did historical controls. Hepatoblastomas (a rare form of hepatocellular carcinoma) were observed in four high-dose male mice along with other hepatocellular carcinomas. This tumor type had not been previously observed in 1,091 male vehicle-control mice in NTP studies. An increase in thyroid gland follicular cell hyperplasia was observed in dosed male mice, and there was a marginal positive trend in the incidence of follicular cell adenomas of the thyroid gland in female mice. The incidence of pheochromocytomas (tumors of chromaffin tissue of the adrenal medulla or sympathetic pregangliar, benign and malignant, combined) of the adrenal gland was 0 of 47 (control), 2 of 48 (low dose) and 3 of 49 (high dose), and the incidence of adrenal gland medullary hyperplasia and focal hyperplasia of the adrenal gland capsule were increased as well in dosed male mice.

The observation that kidney tumors are induced in male, but not female, rats in response to exposure to certain chemicals has been the subject of recent research. It has been hypothesized that the male rat kidney is susceptible to the induction of certain tumors because it contains the protein $\alpha_{2\mu}$-globulin, which has not been found at significant levels in either female rats, or in mice and humans of either sex (Charbonneau et al. 1987, 1989a, 1989b). Chemicals like 1,4-dichlorobenzene, which reversibly bind to this protein, cause the formation of hyalin droplets in the proximal convoluted tubules of male rats. The hyalin droplet-protein complex is resistant to degradation by lysosomal enzymes and accumulates in the tubule, leading to localized hyperplasia of the epithelium (Borghoff et al. 1991; EPA 199 li). It is hypothesized that the resulting cellular damage and cell proliferation enhances tumor formation via a mechanism not yet elucidated. It has also been demonstrated that the same effects can be elicited in male rats administered other $\alpha_{2\mu}$-globulin-binding chemicals such as hexachloroethane, d-limonene [1-methyl-4(l-methylethenyl)-cyclohexene], unleaded gasoline, and pentachloroethane (EPA 1991i). Based on these data, EPA (1991) concluded that tumors associated with $\alpha_{2\mu}$-globulin and hyalin droplets are specific to species that produce this protein in large quantities, and that these tumors should be distinguished from other renal tumors.

The finding of hepatocellular carcinomas and adenomas in mice in the NTP (1987) study has been the subject of scientific debate. There was a high incidence of these tumors in both male and female control animals, but this is fairly common in mice. However, in this case the tumor incidence in the female controls was substantially higher than the historical control value. In addition, 1,4-dichlorobenzene has not been demonstrated to be mutagenic in any of the microbial or mammalian systems tested (NTP 1987), suggesting that the liver tumors are not the result of genotoxicity. Hepatocellular degeneration with resultant initiation of tissue repair was present in both male and female treated mice. This led NTP (1987) to speculate that 1,4-dichlorobenzene acted as a tumor promotor rather than a tumor initiator during the formation of the liver tumors found in male and female mice.

As shown in Table 2-2, 300 mg/kg/day is the cancer effect level (CEL) for renal tubular cell adenomas in male rats and 600 mg/kg/day is the CEL for hepatocellular carcinomas and hepatoblastomas in mice (NTP 1987). A q_1* (the upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure) of $6x10^{-3}$ per mg/kg/day has been calculated from the data on renal tumors in rats (Battelle and Crump 1986). The q_1* for the mouse liver tumor data is $2.4x10^{-2}$ per mg/kg/day (HEAST 1992). These values are currently under review by the EPA (HEAST 1990) and have not been included in the IRIS (1998) database.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to 1,4-dichlorobenzene.

The dermal LD_{50} for 1,4-dichlorobenzene in Sherman rats was greater than 6,000 mg/kg/day (Gaines and Linder 1986). It is not clear how many rats died after dermal exposure to 1,4-dichlorobenzene in this study, and there are no toxicokinetic data that address the question of absorption of 1,4-dichlorobenzene by the dermal route.

2.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans after dermal exposure to 1,4-dichloro-benzene.

Solid 1,4-dichlorobenzene was noted to produce a burning sensation when held closely to the skin for an excessive period of time, but it does not produce irritation or systemic effects (Hollingsworth et al. 1956). One study was located regarding the systemic effects in rabbits after dermal exposure to 1,4-dichlorobenzene (Hollingsworth et al. 1956). However, there was considerable variability in this study regarding the number of animals exposed, and the total number of exposures.

No studies were located regarding the following effects in humans or animals after dermal exposure to 1.4-dichlorobenzene:

2.2.3.3 Immunological and Lymphoreticular Effects
2.2.3.4 Neurological Effects
2.2.3.5 Reproductive Effects
2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer effects in humans or animals after dermal exposure to 1,4-dichlorobenzene.

2. 3 TOXICOKINETICS

Quantitative absorption studies are not available for 1,4-dichlorobenzene in either humans or animals. This compound has some structural similarities to benzene and the smaller chlorinated aliphatics, and is thus assumed to be 100% absorbed when administered orally. Available data on 1,4-dichlorobenzene itself shows that under specific conditions, about 20% was absorbed via inhalation during a 3-hour exposure period. The potential for dermal absorption has not been assessed.

The specific toxicokinetic behavior of 1,4-dichlorobenzene in children (and immature laboratory animals) has not been reported. It is not known if appreciable amounts of 1,4-dichlorobenzene penetrate or adversely affect the parental germ cells (or supporting cellular structures) in humans or laboratory animals; however, the available evidence suggests that 1,4-dichlorobenzene is not genotoxic. It is anticipated that the health effects, absorption, distribution, metabolism, and excretion of 1,4-dichlorobenzene and its metabolites would be quite similar to that of the adult human (or animal). Passage of toxicants across the placental membranes is largely by simple passive diffusion. Given that 1,4-dichlorobenzene is a lipidsoluble toxicant, it is likely to pass across the placental membranes quite easily. The capability of the placenta to metabolize 1,4-dichlorobenzene is not known. It will also likely accumulate in many of the same tissues where it would normally be expected to accumulate in the adult. Li et al. (1995) noted that fetuses have very little body fat and, as such, may not accumulate lipophilic material to the degree of the mother. Extrapolating this information and applying it to the toxicokinetics of 1,4-dichlorobenzene in the fetus/infant, it would be expected that they would not accumulate 1,4-dichlorobenzene in fat to the same degree as the mature animal. As body fat content increases, higher accumulation of 1,4-dichlorobenzene would be anticipated.

1,4-Dichlorobenzene and other isomers of dichlorobenzene have been found in human breast milk (EPA 1983b; Erickson et al. 1980; Pellizzari et al. 1982). It is expected that some amount of 1,4-dichlorobenzene would accumulate in human breast milk, given its high lipid (milk fat) content. 1,4-Dichlorobenzene is classified as an organochlorine compound and, as such, shares many of the biochemical characteristics of this class of chemicals, which includes high lipid solubility. A few studies have noted that 1,4-dichlorobenzene will preferentially distribute to adipose tissues in relatively high amounts, compared to accumulations in the liver and kidneys (Hawkins et al. 1980; Charbonneau et al. 1989b; Klos and Dekant 1994). Loss of maternal body fat may mobilize 1,4-Dichlorobenzene from fat storage deposits in exposed mothers. This mobilization could result in increased blood levels and/or excretion of 1,4-dichlorobenzene and its metabolites from the mother, as well as redistribution to other fat deposition sites, such as the high fat content found in breast milk.

The toxicokinetics of 1,4-dichlorobenzene are described below.

Animal studies have demonstrated that 1,4-dichlorobenzene, once absorbed, is highly concentrated in adipose tissue, with much lower levels in liver and kidney. Detectable levels have also been reported in blood, lung, heart, and brain.

2,5-Dichlorophenol has been demonstrated to be the major urinary metabolite of 1,4-dichlorobenzene in both humans and animals. This metabolite is eliminated principally as a conjugate of glucuronic or sulfuric acid. Some elimination in feces and expired air has been observed, and there is also evidence of reabsorption through the enterohepatic circulation and excretion in bile.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the rate or amount of absorption of 1,4-dichlorobenzene by humans or animals after inhalation exposure to 1,4-dichlorobenzene.

CFA rats were exposed by inhalation to ^{14}C-1,4-dichlorobenzene at 1,000 ppm 3 hours per day for 10 days (Hawkins et al. 1980). Based on a body weight of 200 g for rats in this study and a breathing rate of

0.34 m^3/day (EPA 1985a), these rats absorbed approximately 20% of the administered dose. Because a 3-hour per day exposure regimen was used in the inhalation studies, it is not possible to make comparisons with results observed in the more commonly used 6-8-hour per day inhalation exposure regimens.

2.3.1.2 Oral Exposure

No studies were located that specifically address the rate or amount of absorption of 1,4-dichlorobenzene by humans or animals after oral exposure to 1,4-dichlorobenzene. Based on the absorption rates of benzene and the smaller chlorinated aliphatics, EPA (1987a) has assumed that 100% of an oral dose of 1,4-dichlorobenzene is absorbed. This assumption is supported by data that demonstrate that tissue levels of ^{14}C are similar in female rats that have received ^{14}C-1 ,6dichlorobenzene at 250 mg/kg/day for 10 days via gavage or by subcutaneous injection (Hawkins et al. 1980).

2.3.1.3 Dermal Exposure

No studies were located that specifically address the rate or amount of absorption of 1,4-dichlorobenzene by humans or animals after dermal exposure to 1,4-dichlorobenzene. Solid 1,4-Dichlorobenzene produces a burning sensation when held closely to the skin for an excessive period of time, but it does not produce irritation or systemic effects (Hollingsworth et al. 1956). This observation indicates that some of the chemical must penetrate the skin to produce an effect on nerve endings in the skin. In a study of the acute dermal toxicity of 1,4-dichlorobenzene in adult Sherman rats, the dermal LD_{50} was estimated to be greater than 6,000 mg/kg/day in both sexes (Gaines and Linder 1986). Assuming there were no incidental oral or inhalation exposures, these data do not conclusively indicate that 1,4-dichlorobenzene is absorbed to any extent after dermal exposure; if dermal exposure does occur, it is associated with low systemic toxicity in both humans laboratory animals.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the tissue distribution of 1,4-dichlorobenzene in humans after inhalation exposure to 1,4-dichlorobenzene. The compound has been found, however, in human blood, fatty tissue,

and breast milk, presumably as a result of exposure via inhalation. In a study of Tokyo residents, detectable levels of 1,4-dichlorobenzene were found in all of 34 adipose tissue samples and all of 16 blood samples tested (Morita and Ohi 1975; Morita et al. 1975). In a national survey of various volatile organic compounds (VOC) found in composites of human adipose tissue, samples were collected from persons living in the nine geographic areas that comprise the United States (within this survey). The specimens (subcutaneous, perirenal, or mesenteric adipose tissue) were collected from October 1981 through September 1982 and were excised during surgery or as part of postmortem examinations. For each geographic location, three age groups were represented: 0-14 years, 15-44 years, and 45 or more years. Positive results were reported for 1,4-dichlorobenzene in these composites in every category of analysis, with levels ranging from 0.012 to 0.50 μg/g wet tissue (EPA 1986c. In human milk samples collected from 42 lactating women in five locations in the eastern United States, measured values of 1,4-Dichlorobenzene ranged from 0.04 to 68 μg/mL with an average of 9.15 μg/mL (EPA 1983b).

In animal studies, the tissue distribution of ^{14}C-1,4-dichlorobenzene in female CFY rats was found to be similar following inhalation, oral, and subcutaneous exposure (Hawkins et al. 1980). The inhalation exposure regimen was 10 consecutive days of exposure to ^{14}C-1,4-dichlorobenzene at 1,000 ppm for 3 hours per day, and the highest concentrations of ^{14}C were measured in fat (up to 557 μg/g via inhalation) and next highest levels in kidneys and liver. Concentrations in kidney and liver were about 5-10% of that found in adipose tissue, irrespective of the route of exposure. Distribution patterns for all routes were also similar to those observed by Kimura et al. (1979) using the oral route, as described below.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of 1,4-Dichlorobenzene in humans after oral exposure to 1,4-dichlorobenzene.

Several studies in animals clearly demonstrate that adipose tissue is a major sink for ingested 1,4-dichloro-benzene. In male rats that received a single gavage dose of 200 mg/kg/day, the highest concentration of 1,4-dichlorobenzene was found in adipose tissue, peaking at 800 ppm 12 hours after exposure, and was present in decreasing quantities at all sampling intervals up to 120 hours postexposure in the adipose tissue (Kimura et al. 1979). Kidney (30 ppm) and liver (23 ppm) contained the next highest levels of 1,4-dichlorobenzene. Low levels of 1,4-dichlorobenzene were also found in blood, lung, heart, and brain.

Most of the 1,4-dichlorobenzene in all tissues except for adipose had disappeared within 48 hours after administration of the chemical. Low levels of 1,4-dichlorobenzene were still detected in the adipose tissue after 120 hours. Similar results were obtained in male rats administered a single 500 mg/kg/day dose of ^{14}C-1,4-dichlorobenzene by gavage in corn oil and sacrificed 24 hours after dosing (Charbonneau et al. 1989b).

In another study in which male and female Fisher 344 rats were administered a single dose of 900 mg/kg/day ^{14}C-1,3-dichlorobenzene by gavage in corn oil and sacrificed at 72 hours, the percentage of the dose found in tissues and excreta from males was: tissues (all organs pooled), 0.05%; fat, 0.1%; blood, 0.04%; feces, 3.6%; and urine, 41.3%. Thus, more than half (55%) of the dose was probably exhaled; 60% was not accounted for. In females recovery of radioactivity was: tissue, 0.04%; fat, 0.1%; blood, 0.03%; feces, 2.5%; and urine, 37.8%. In the tissues examined, the radioactivity bound to protein was below the detection limit (Klos and Dekant 1994). Charbonneau et al. (1987) reported that 49.8% of l,4-dichloro-benzene-equivalent was in the kidney cytosol of male Fischer 344 rats administered a single dose of 300 or 500 mg/kg/day ^{14}C-1,4-dichlorobenzene by gavage in corn oil and sacrificed 24 hours after dosing. Fat samples were not analyzed for 1,4-dichlorobenzene.

In female rats that received gavage doses of 50-500 mg/kg/day for 10 days, distribution patterns were similar to those observed by Kimura et al. (1979) and Charbonneau et al. (1989b), as described above, with the highest concentrations measured in fat and the next highest, but much lower, levels in kidney and liver (Hawkins et al. 1980).

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of 1,4-dichlorobenzene in humans or animals after dermal exposure to 1,4-dichlorobenzene.

2.3.3 Metabolism

2,5-Dichlorophenol appears to be the principal metabolic product of 1,4-dichlorobenzene in both humans and laboratory animals. The metabolism of 1,4-dichlorobenzene appears to involve both phase I and phase II metabolism pathways.

Analysis of the urine specimens of a 3-year-old boy who had been playing with 1,4-dichlorobenzene yielded 2,5dichlorophenol as well as 4 other unidentified phenols. These compounds were shown to be conjugated with glucuronic and sulfuric acids (Hallowell 1959).

In adult female CFY rats exposed by inhalation (whole-body) to nominal concentrations of 1,000 ppm ^{14}C-1,4-dichlorobenzene, 3 hours a day for 10 days, analysis of metabolites in urine indicated that more than 50% was a sulfate of 2,5dichlorophenol, and much of the rest was a glucuronide conjugate of 2,5-dichlorophenol. A minor component was a dihydroxydichlorobenzene, assumed by the authors to be 2,5-dichloroquinol. Analysis of bile revealed the same metabolites, but with quantitative differences (Hawkins et al. 1980).

Following oral administration to Chinchilla rabbits, 1,4-dichlorobenzene was also oxidized, principally to 2,5-dichlorophenol. A very high percentage of this metabolite was eliminated in the urine as conjugates of glucuronic or sulfuric acids (Azouz et al. 1955).

Male Wistar rats given single oral doses of 10, 50, or 250 mg/kg of ^{14}C-1,4-dichlorobenzene (vehicle not given) excreted the majority of ^{14}C derived from 1,4-dichlorobenzene in the urine as either the sulfate conjugate (60%) or the glucuronide (30%). Bile contained 5 and 30% of the total radioactivity after the low and high doses, respectively. Only minor amounts of mercapturic acid were found (Hissink et al. 1997).

The excretion of 1,4-dichlorobenzene and metabolites was examined in male rats administered a single dose of 200 mg/kg 1,4-dichlorobenzene given by gavage in corn oil and monitored up to 120 hours after dosing (Kimura et al. 1979). Within 12 hours after dosing, 2 sulfur-containing metabolites, 2,5-dichlorophenyl methyl sulfoxide, and 2,5-dichlorophenyl methyl sulfone (M2), were found in the blood, urine, fat, liver, and kidneys. These metabolites remained in the blood after most of the 1,4-dichlorobenzene had fallen below the detection limits of the assay. The maximum concentration of 2,5-dichlorophenyl methyl sulfoxide in blood was reached 15 hours after dosing and declined rapidly thereafter. For 2,5-dichlorophenyl methyl sulfone, 2 peaks were detected at 18 and 48 hours after dosing, which suggested to the authors that 2,5-dichlorophenyl methyl sulfone might undergo enterophepatic circulation. Changes in the levels of these metabolites in blood and tissues over a 120-hour period led the authors to suggest that 2,5-dichlorophenyl methyl sulfone might arise from 2,5-dichlorophenyl methyl sulfoxide.

In a later study, male and female Fisher 344 rats were administered a single dose of 900 mg/kg/day ^{14}C-1,4-dichlorobenzene by gavage in corn oil, the excretion of radioactivity in the urine reached a peak both in males and females between 24 and 36 hours after dosing. The major urinary metabolite was 2,5dichlorophenol, mostly in the form of sulfate and glucuronide conjugates. 2-(N-acetyl-cysteine-S-yl)-2,3-dihydro-3-hydroxy-1,3-hydroxy-1,4-Dichlorobenzene and 2-(N-acetyl-cysteine-S-yl)-1,4-dichlorobenzene were minor metabolites in the urine from both males and females. Minor amounts of 2,4-dichlorohydroquinone were excreted as an unidentified conjugate. A mercapturic acid of chlorophenol also appeared to be formed and excreted in the urine. The latter compound would result from the reaction of glutathione (GHS) with a 3,4-epoxide of 1,4-dichlorobenzene. Quantification of the metabolites in the urine 72 hours after a single 1,000 mg/kg/day oral dose of 1,4-Dichlorobenzene showed about 17% of the dose as 2,5-dichlorophenol after acid hydrolysis; 1.1% in males and 1.4% in females as 2,5-dichloro-hydroquinone, also after acid hydrolysis; and 0.4% in males and 1.4% in females as 2-(N-acetylcysteine-S-yl)-1,4-dichlorobenzene. The mercapturic acid of chlorophenol and 2-(N-acetyl-cysteine-S-yl)-2,3-dihydro-3-hydroxy-1,3-hydroxy-l,6dichlorobenzene could not be quantified. Male rats excreted the conjugates of 2,5dichlorophenol and 2,5-dichlorohydroquinone in greater amounts than females. The opposite was true for 2-(N-acetyl-cysteine-S-yl)-1,4-dichlorobenzene. However, these differences were minor (Klos and Dekant 1994).

The mechanism of 1,4-dichlorobenzene oxidation to 2,5-dichlorophenol has not yet been thoroughly investigated. The metabolism of 1,4-dichlorobenzene could involve the formation of an arene oxide intermediate, as has been proposed to occur in the oxidative metabolism of many halogenated aromatic hydrocarbons (Jerina and Daly 1974). 1,4-Dichlorobenzene has not been shown to be mutagenic in microbial or mammalian systems; this is perhaps suggestive evidence that a (mutagenic) arene oxide intermediate is not involved in its metabolism.

Fischer et al. (1995) compared the metabolism and toxicity of the dichlorobenzene isomers in liver slices prepared from human donor tissues, and from male Sprague-Dawley and Fischer 344 rats. At 2 and 6 hours, the metabolism of 1,4-Dichlorobenzene in human liver slices was similar to that seen in Sprague-Dawley and Fischer 344 rats. In human and Fischer 344 rat liver slices, the metabolism of 1,4-dichlorobenzene was intermediate to that of 1,3- and 1,2-dichlorobenzene at 2 hours; at 6 hours the metabolism of 1,4-dichlorobenzene was lower than that of 1,3- or 1,2-dichlorobenzene. In Sprague-Dawley rats, the hepatic metabolism of 1,4-dichlorobenzene was greater than that of 1,3- and 1,2-dichlorobenzene at

2 hours, while at 6 hours, the metabolism of 1,4-dichlorobenzene was intermediate to that of 1,3- or 1,2-dichlorobenzene. In all 3 species, the metabolism of 1,4-dichlorobenzene was not linear over time; the amount metabolized at 6 hours was only slightly higher than that metabolized after 2 hours. At both 2 and 6 hours, the amount of glucuronide and sulfate conjugates produced from 1,4-Dichlorobenzene was similar across all of the tested species.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans after inhalation exposure to 1,4-dichlorobenzene.

In an animal study, inhaled 1,4-Dichlorobenzene was excreted mainly in the urine. When ^{14}C-1,4-dichlorobenzene was administered to female rats for 10 days via inhalation at 1,000 ppm for 3 hours per day, 97.4% of the total excreted ^{14}C activity was recovered in the urine. The amount of ^{14}C-label excreted in the expired air during 48 hours after the tenth dose represented a small proportion of the total ^{14}C excreted (Hawkins et al. 1980). This level was similar after inhalation (0.2%) and oral (1%) exposure. In rats with cannulated bile ducts, no ^{14}C was detected in the feces up to 24 hours after inhalation exposure or after a single subcutaneous dose. Of the total ^{14}C recovered, 48.5% was eliminated in the bile and 51.5% in the urine. The lower level of ^{14}C excretion in the urine of cannulated rats than of noncannulated rats indicated that in noncannulated rats, much of the label that was eliminated in the bile was reabsorbed and ultimately excreted in the urine.

2.3.4.2 Oral Exposure

No studies were located on excretion in humans after oral exposure to 1,4-Dichlorobenzene.

Based on a study in animals, orally administered 1,4-dichlorobenzene appears to be excreted mainly in the urine as metabolites. Male Wistar rats given single oral doses of 10, 50, or 250 mg/kg of ^{14}C-1,4-dichlorobenzene excreted the majority of ^{14}C derived from 1,4-dichlorobenzene in the urine as either the sulfate conjugate (60%) or the glucuronide (30%). Bile contained 5 and 30% of the total radioactivity after the low and high doses, respectively. Only minor amounts of mercapturic acid were found (Hissink et al.

1996). In a later study (Hissink et al. 1997), the kinetics and biotransformation of 1,4-dichlorobenzene and the influence of pretreatment with isoniazid, a CYP2El inducer (the main cytochrome P-450 isoenzyme involved in the biotransformation of 1,4-dichlorobenzene), was studied. Groups of adult male Wistar rats were cannulated and dosed via gavage with 10 (n=2), 50 (n=4), or 250 (n=4) mg/kg body weight radiolabeled 1,4-dichlorobenzene dissolved in corn oil. Excretion was again predominantly via urine (78-85%) and to a smaller degree via feces (2-5%). The relative contributions of these routes were not dose-dependent. Excretion via bile ranged from less than 5% at the low-dose level to 30% at the high-dose level. The major biliary metabolite was the glucuronide of 2,5-dichlorophenol. 1,4-Dichlorobenzene was mainly metabolized to 2,5-dichlorophenol (approximately 90%), which was detected in the urine as its sulfate (50-60%), glucuronide (20-30%), and in its free form (5-10%). Minor metabolites were N-acetyl-cysteine-S-dihydro-hydroxy-1,4-dichlorobenzene and the corresponding dehydrated N-acetyl-cysteine-S-1,4-dichlorobenzene, which comprised about 10% of total metabolites. No hydroquinones were observed in the male Wistar rat, even under conditions of induced oxidative metabolism using isoniazid as the CYP2El inducer. It also was noted that induction of CYP2El by isoniazid tended to result in a smaller area under the curve (AUC) for blood concentration, a corresponding higher clearance of 1,4-Dichlorobenzene, and a more rapid urinary excretion of metabolites. The authors also could not rule out the role of CYP2B in 1,4-dichlorobenzene metabolism.

The excretion of 1,4-Dichlorobenzene and metabolites was examined in male Wistar rats administered a single dose of 200 mg/kg 1,4-dichlorobenzene by gavage in corn oil and monitored up to 120 hours after dosing (Kimura et al. 1979). Within 12 hours after dosing, 2 sulfur-containing metabolites, 2,5-dichlorophenyl methyl sulfoxide and 2,5-dichlorophenyl methyl sulfone, were found in the urine. Over a 96-hour period, 46% of the dose was excreted as 2,5dichlorophenol, the major metabolite of 1,4-dichlorobenzene; only 0.031 and 0.122% of the dose was excreted in the urine as 2,5-dichlorophenyl methyl sulfoxide and 2,5-dichlorophenyl methyl sulfone, respectively. The authors also mentioned that 2,5-dichlorophenyl methyl sulfoxide and 2,5-dichlorophenyl methyl sulfone were detected in the urine from rats dosed with 800 mg/kg 1,4-Dichlorobenzene for 1 week, but no experimental details were provided.

Chinchilla rabbits gavaged once with 500 mg/kg/day 1,4-dichlorobenzene in olive oil excreted 35% of the administered dose in the urine as 2,5-dichlorophenol. Another 6% of the administered dose was excreted in the urine as 2,5-dichloroquinol. At 6 days after dosing, urinary excretion of 1,4-dichlorobenzene

metabolites was still in progress; however, fecal excretion could not be detected during the 6-day monitoring period (Azouz et al. 1955).

In male and female Fischer 344 rats administered a single dose of 900 mg/kg/day ^{14}C-1,4-dichlorobenzene by gavage in corn oil, the excretion of radioactivity in the urine reached a peak in both males and females between 24 and 36 hours after dosing. Seventy-two hours after dosing, 41.3 and 3.6% of the dose was found in the urine and feces, respectively, of males; corresponding values in the urine and feces of females were 41.3 and 3.6%, respectively (Klos and Dekant 1994).

When ^{14}C-1,4-dichlorobenzene was administered by gavage to female rats for 10 days at 250 mg/kg/day, 97% of the recovered ^{14}C was eliminated in the urine within 5 days post-treatment. Approximately 1% was recovered in expired air (Hawkins et al. 1980). In rats with cannulated bile ducts, only 9% of the recovered ^{14}C was excreted in the feces during the 24 hours following the last dose and was presumed to be unabsorbed material. Another 63% was recovered in the bile and 28.1% in the urine. The lower level of ^{14}C excretion in the urine of cannulated rats than in that of noncannulated rats indicated that in noncannulated rats, much of the label that was eliminated in the bile was reabsorbed or metabolized and ultimately excreted in the urine.

2.3.4.3 Dermal Exposure

No studies were located on excretion in humans or animals after dermal exposure to 1,4-dichlorobenzene.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

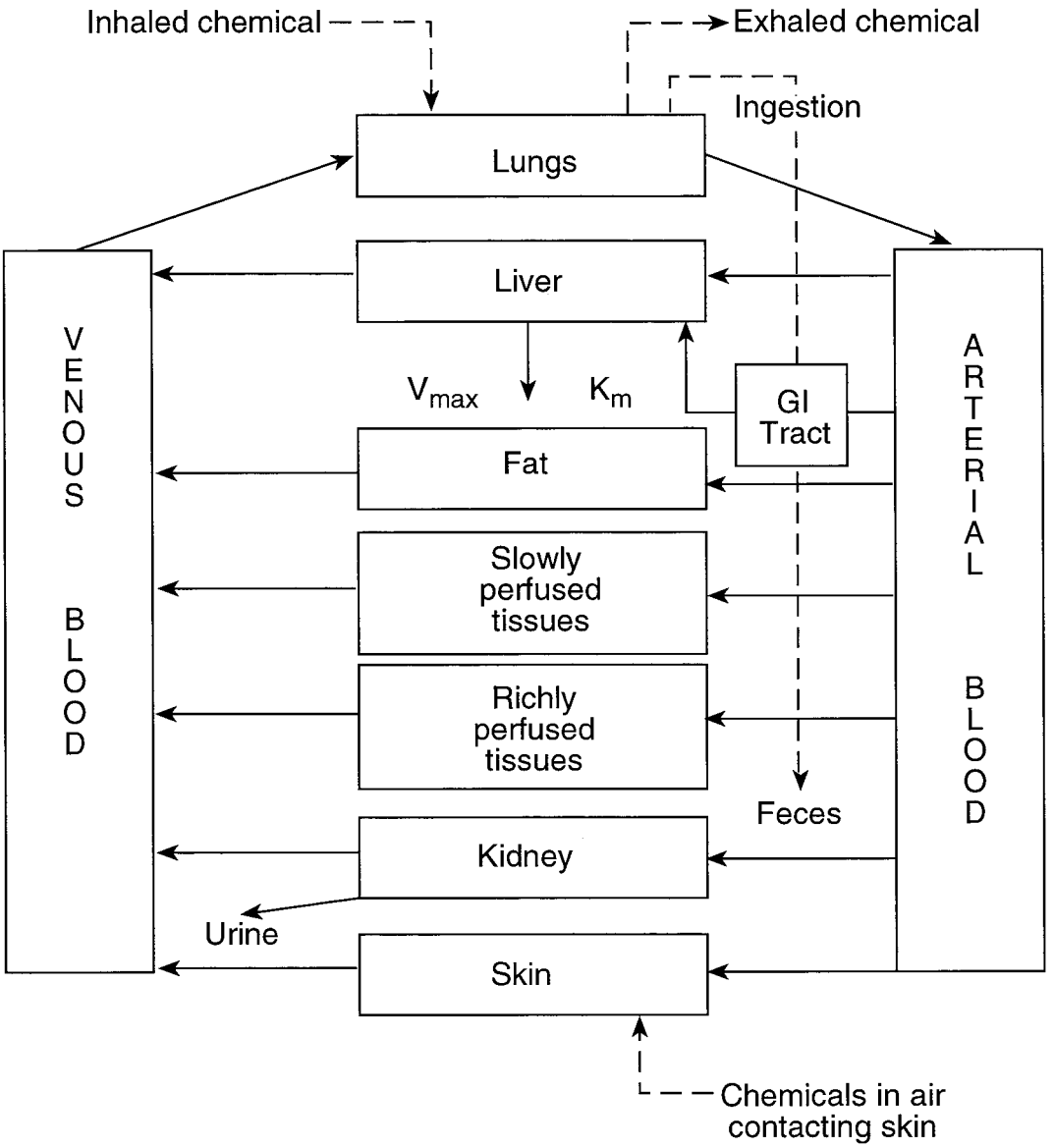
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species.
Figure 2-3 shows a conceptualized representation of a PBPK model.

Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

If PBPK models for 1,4-dichlorobenzene exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK models were identified for 1,4-dichlorobenzene.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption. Quantitative inhalation, oral, or dermal absorption studies in humans are not available for 1,4-dichlorobenzene. In the few studies available in laboratory animals, absorption was demonstrated to occur during a 3-hour inhalation exposure to 1,000 ppm of 1,4-dichlorobenzene (Hawkins et al. 1980) as evidenced by accumulation of ^{14}C in liver, kidney, plasma, and adipose tissue. No studies were located that described the absorption characteristics of 1,4-dichlorobenzene after oral exposure; however, given the structural and physicochemical similarity to benzene, oral absorption is thought to be at or near 100% (EPA 1987a; Hawkins et al. 1980). A study assessing dermal absorption reported a dermal LD_{50} of >6,000 mg/kg/day in rats (Gaines and Linder 1986). Given the physicochemical properties, similarity to benzene, and lipid-soluble properties of 1,4-dichlorobenzene, absorption by the inhalation, oral, and dermal routes of exposure is most likely by simple diffusion across cellular lipid membranes. No information is available that describes site-specific absorption within the respiratory tract (nasal epithelial absorption as opposed to alveolar absorption) or in the gastrointestinal tract.

Distribution. Quantitative inhalation, oral, or dermal distribution studies in humans are not available for 1,4-dichlorobenzene. 1,4-Dichlorobenzene has been detected in human blood, adipose tissue, and breast milk after an assumed inhalation exposure in Tokyo residents (Morita and Ohi 1975; Morita et al. 1975), as well as people in some parts of the United States (EPA 1983b, 1986). The available data indicate that after inhalation, oral, and subcutaneous exposure, 1,4-dichlorobenzene preferentially distributes to the fat tissue and organ-specific sites within the body (Hawkins et al. 1980), following the order: adipose > kidney > liver > blood (Charbonneau et al. 1989b; Hawkins et al. 1980). Although 1,4-dichlorobenzene is originally distributed primarily to adipose tissue, significant amounts of 1,4-dichlorobenzene are not retained in that tissue after exposure ceases (see Chapter 3). Regardless of exposure route, most of the

1,4-dichlorobenzene falls to near- or below-detectable assay limits in all tissues of the body except adipose tissues 48-72 hours after exposure, depending on the dose (Charbonneau et al. 1989b; Kimura et al. 1979). 1,4-Dichlorobenzene was detected in adipose tissue at 120 hours after exposure (Charbonneau et al. 1989b). In the kidney, 50% of the 1,4-dichlorobenzene appears to localize within the cytosol in male Fischer 344 rats (Charbonneau et al. 1987). 1,4-Dichlorobenzene also does not appear to bind to tissue proteins (Klos and Dekant 1994).

Metabolism/Excretion. Quantitative inhalation, oral, or dermal metabolism and excretion studies in humans are not available for 1,4-dichlorobenzene. One case study involving a 3-year-old boy who may have ingested 1,4-dichlorobenzene reported the presence of 2,5-dichlorophenol in the urine (Hallowell 1959). Several laboratory animal studies have indicated that 1,4-dichlorobenzene is metabolized by phase I metabolism to 2-5-dichlorophenol (probably by cytochrome P-450), which then undergoes phase II metabolism/conjugation to the glucuronide or sulfate (Azouz et al. 1955; Hawkins et al. 1980; Hissink et al. 1996; Kimura et al. 1979; Klos and Dekant 1994). Minor amounts of 2,4-dichlorohydroquinone may also be present (Klos and Dekant 1994). Metabolism occurs in the liver. None of the detected metabolites have been reported to be associated with the toxic effects seen with 1,4-dichlorobenzene. Metabolites are excreted mostly in the urine (Azouz et al. 1955; Hissink et al. 1996; Kimura et al. 1979); however, some metabolites (mainly the glucuronide conjugate) may also be excreted in the bile and feces (Hissink et al. 1996). The role of enterohepatic circulation in the metabolism and excretion of metabolites is not completely known; however, it has been suggested that enterohepatic circulation may occur with some sulfated metabolites (Kimura et al. 1979). This phase I and II metabolic pathway mechanism (see below) seems plausible, in that other chemicals with similar (halogenated- and lipid-soluble) physicochemical properties undergo very similar metabolic routines to become more water-soluble and excreted. The data suggest that metabolism and excretion are similar in several species. It is likely that human metabolic pathways are similar, if not identical, to those established in laboratory animals.

2.4.2 Mechanisms of Toxicity

The precise mechanism of 1,4-dichlorobenzene oxidation to 2,5-dichlorophenol has not thoroughly been investigated. 1,4-Dichlorobenzene is known to be metabolized by cytochrome P-450 (Azouz et al. 1955; Hawkins et al. 1980) in order to be presented to phase II metabolic pathways to increase its water solubility for excretion. A proposed metabolic pathway involving cytochrome P-450 with intermediate formations of metabolites has been outlined for 1,4-dichlorobenzene (Den Besten et al. 1992). No information was

available regarding specific or altered mechanisms of action for 1,4-dichlorobenzene in children. The hepatotoxicity and nephrotoxicity observed in laboratory animals are likely due to the formation of toxic intermediates formed while converting 1,4-dichlorobenzene to 2,5dichlorophenol by cytochrome P-450, or by depletion of GSH at higher doses of 1,4-dichlorobenzene, or both. Some indirect evidence of this was provided by Mizutani et al. (1994). In mice pretreated with DL-buthionine sulfoximine (BSO), a glutathione synthesis inhibitor, a single dose of 300 mg/kg 1,4-dichlorobenzene caused significant elevations of ALT and liver calcium, both peaking between 24 and 32 hours after dosing and declining thereafter, indicative of hepatic damage. Necrotic changes were observed at those times as well as hemorrhage, fatty changes, and appearance of altered eosinophilic cells. A single 1,200 mg/kg dose of 1,4-dichlorobenzene did not significantly alter ALT or liver calcium, but doses of 100 mg/kg or higher in mice pretreated with BSO produced dose-related alterations in these parameters. Increasing cellular GSH with GSH monoethyl ester protected the liver from the combination of 1,4-dichlorobenzene and BSO. In addition, pretreatment with microsomal cytochrome P-450-dependent monooxygenase inhibitors also protected the liver from the combined toxicity of 1,4-dichlorobenzene and BSO. Pretreatment with the P-450 inducer beta-naphthoflavone did not significantly alter the effect of 1,4-dichlorobenzene plus BSO. Pretreatment with phenobarbital partially blocked the effect of 1,4-dichlorobenzene plus BSO on ALT and completely prevented the increase in liver calcium. PCBs prevented the effect on both ALT and liver calcium. Treatment with BSO alone or in combination with 1,4-dichlorobenzene (300 mg/kg) greatly decreased hepatic GSH concentration, the effect being more pronounced with the combination. 1,4-Dichlorobenzene alone had no such effect. Depletion of GSH also has been reported to increase the toxicity of 1,4-dichlorobenzene in rats (Stine et al. 1991). The data provide a strong indication that the mechanism behind the hepatic (and probably renal) toxicity of 1,4-dichlorobenzene lies in the intermediate steps of metabolite formation and conjugation by cytochrome P-450. Formation of 2,5-dichlorophenol from 1,4-dichlorobenzene via cytochrome P-450 metabolism likely produces some intracellular, intermediate metabolite(s) that are also hepatotoxic when sufficient amounts accumulate intracellularly. These yet unidentified metabolites are detoxified by GSH; but when GSH depletion occurs, which is likely to occur at higher oral doses, toxicity is enhanced. Hepatocytes respond to these insults by releasing intracellular enzymes (Carlson and Tardiff 1976; Umemura et al. 1996), degeneration, vacuolation (Eldridge et al. 1992; NTP 1987; Rimington and Ziegler 1963), necrosis, and increases in gross liver weight (Hollingsworth et al. 1956; Riley et al. 1980). However, these changes are not specific to 1,4-dichlorobenzene and likely occur in a dose-responsive manner. At lower doses, cellular proliferation in the liver in the absence of these toxic-type responses have been observed (Eldridge et al. 1992; Umemura et al. 1996); however, the mechanism behind this response needs to be more clearly defined. Exposure to 1,4-dichlorobenzene likely follows similar metabolic pathways in the kidneys and would be responsible for

the toxicity (increased organ weight, tubular degeneration, nephropathy) observed in that organ, and may also be linked to the known formation of cancer-linked micro globulins ($\alpha_{2\mu}$-globulin) in male rats.

The metabolism of 1,4-dichlorobenzene could involve the formation of an arene oxide intermediate, as has been proposed to occur in the oxidative metabolism of many halogenated aromatic hydrocarbons (Jerina and Daly 1974). 1,4-Dichlorobenzene has not been shown to be mutagenic in microbial or mammalian systems, a result that may be viewed as further suggestive evidence that an arene oxide intermediate is not involved in its metabolism.

1,4-Dichlorobenzene has also been reported to produce hematological effects associated with exposure in humans and laboratory animals. These findings have been limited to red and white blood cell anomalies (NTP 1987) in rats and mice, and may take place within the bone marrow at the time of red and white cell formation, although a precise and careful mechanism behind this finding has not been produced. Acute hemolytic anemia and methemoglobinemia reportedly occurred in a 3-year-old boy who had played with, and possibly ingested, 1,4-dichlorobenzene crystals (Hallowell 1959). A 21-year-old pregnant woman who had eaten 1-2 blocks of 1,4-dichlorobenzene toilet air freshener per week throughout pregnancy developed severe microcytic, hypochromic anemia with excessive polychromasia and marginal nuclear hyper-segmentation of the neutrophils. Heinz bodies were seen in a small number of the red cells. After she discontinued this practice (at about 38 weeks of gestation), her hemoglobin levels began to rise steadily. The mechanism behind these findings in the human exposures are unknown, but it appears that 1,4-dichlorobenzene may have some local effect on the hemoglobin content of the red blood cell (hemolysis, methemoglobinemia, Heinz bodies). These are rare events in humans and only occur at very high exposure doses in laboratory animals. The clinical finding of Heinz-body formation in red blood cells and methemoglobinemia suggest that some form of oxidative stress is occurring to produce these findings, although the mechanisms behind these end points are not known. While there may not be any direct evidence, it is not unreasonable to suspect that oxidant metabolites of 1,4-dichlorobenzene may inhibit glucose-6-phosphate dehydrogenase (G6PD), as do metabolites of aniline, leading to Heinz body production, methemoglobinemia, and hemolysis (Trieff et al. 1993). The effect on the red and white blood cell production processes in the bone marrow (anemia, polychromasia) is quite likely an effect related to blood loss associated with bleeding from esophageal varices which form secondary to liver cirrhosis.

2.4.3 Animal-to-Human Extrapolations

No studies were identified that specifically addressed the use of animal data applied to human exposure issues specifically related to 1,4-dichlorobenzene. No physiologically based pharmacokinetic models are available to estimate risk associated with human exposure to 1,4-dichlorobenzene. It is difficult to compare the toxicity of 1,4-dichlorobenzene in laboratory animals to the toxicity observed in humans, since little reliable human data are available for examination (see Section 2.2). From the little data available, it appears that humans do have the potential to exhibit the same toxicological features of 1,4-dichlorobenzene toxicosis as demonstrated or observed in the laboratory animal models studied. Although the mechanisms have not been outlined, human hematological responses (Campbell and Davidson 1970) and liver responses (Hallowell 1959) to 1,4-dichlorobenzene have been similar to the responses of laboratory animals tested (Hollingsworth et al. 1956; NTP 1987). (However, the human hematological responses were vague and quite possibly unrelated.) Although the data are not sufficient to make direct comparisons, the possibility strongly exists that human responses may be similar to those of laboratory animals, and animal data should be taken into consideration until better human data become available. With the exception of the $\alpha_{2\mu}$-globulin observation in the male rat kidney (Bornhard et al. 1988), all of the detoxication pathways present in the laboratory animal models are present in humans. This means that humans are likely to detoxify 1,4-dichlorobenzene in a similar or identical manner to that of the laboratory animals, and suggests that humans are susceptible to the liver and possibly the renal lesions outlined for the laboratory animals studied (see Section 2.4.2). Due to the lack of acceptable dosing and exposure data in humans, it is not possible at present to definitively determine the magnitude of these human toxicological responses, the dose-response relationship, or whether humans are more or less susceptible to these effects on a mg/kg/day (oral and dermal) or ppm (inhalation) basis. It is also unknown whether the sex predilection found in male rats to 1,4-dichlorobenzene renal or endocrine toxicity occurs in the human male.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

As discussed in Section 2.2.1, most human exposure to 1,4-dichlorobenzene results from inhalation of vapors due to home use of mothballs and deodorizer blocks that contain this chemical. Exposure resulting from all other sources, including proximity to hazardous waste sites, is considered to be low. Based on a

combination of available human case studies and experiments with laboratory animals, the major public health concerns associated with exposure to 1,4-dichlorobenzene are effects on the liver, kidneys, and blood. Some immunological, dermatological, and neurological effects have also been reported in exposed humans. There is information from animal studies which raises the question of whether 1,4-dichlorobenzene can cross the placenta and elicit structural effects on the developing fetus. Data from a study conducted in rats using the intraperitoneal route have demonstrated sperm abnormalities. Cancer of the liver as a result of lifetime exposure to 1,4-dichlorobenzene has been shown in mice, and renal cancer has been reported in male rats. However, recent studies related to the mechanism of renal carcinogenesis in rats suggest that these tumors may not be expected to occur in exposed humans. Issues relevant to children are explicitly discussed in Section 2.6, Children's Susceptibility, and Section 5.6, Exposures of Children.

In addition, several studies in animals have demonstrated that increased mortality can result from acute-, intermediate-, or chronic-duration oral exposure to 1,4-dichlorobenzene. Because 1,4-dichlorobenzene mothballs are used in many homes, they are often readily accessible in closets and storage areas. Therefore, there is a potential concern for the lethal effects of 1,4-dichlorobenzene, especially if accidentally consumed by young children.

Minimal Risk Levels for 1,4-Dichlorobenzene

Inhalation MRLs.

- An MRL of 0.8 ppm has been derived for acute-duration inhalation exposure (less than 14 days) to 1,4-dichlorobenzene.

This MRL was calculated using a NOAEL of 300 ppm based on the absence of significant developmental effects in rabbits (Hayes et al. 1985). The NOAEL of 300 ppm was converted to 75 ppm after incorporating adjustments for intermittent exposure (6 hours a day). The NOAEL was further adjusted for Human Equivalent Concentration ($NOAEL_{HEC}$) using Equation 4-48a of EPA (1994k) and by applying an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). In this study, groups of inseminated New Zealand White rabbits were exposed whole body to 0 (filtered air), 100,300, or 800 ppm p-DCB 6 hours a day on Gd 6-18. Vapors of p-DCB were generated by passing air through glass tubes packed with pieces of p-DCB. Sacrifices were conducted on Gd 29. End points examined included maternal body weight and liver and kidneys weights. Fetal observations included

number and position of fetuses *in utero,* number of live or dead fetuses, number and position of resorption sites, number of corpora lutea, sex, body weight and crown-rump length of the fetuses, gross external alterations, and soft tissue and skeletal alterations. Dams in the 800 ppm exposure group gained less weight than did controls during the exposure period. However, after day 18, they rapidly recovered and the final body weight and weight gains were similar to those of controls. There were no effects on absolute or relative maternal liver or kidney weights. At 300 ppm, there was a significant increase ($p<0.05$) in the percentages of resorbed implantations and litters with resorptions. Results at 800 ppm, however, were comparable to controls. At 800 ppm, there were nonsignificant increases in the incidence of acephaly (headlessness), omphalocele (umbilical hernia), and forelimb flexure. Other deformities found only in the offspring of that exposure group were shortened long bones, an extra rib fused to the tenth rib, and a right subclavian artery originating off the pulmonary trunk. A statistically significant increase ($p<0.05$) in the incidence of retroesophageal right subclavian artery was noted in the offspring; however, this effect was considered by the authors not to be a major malformation and had been previously observed in 2% of the litters of control rabbits in that laboratory. The authors concluded that under the conditions of this study, p-DCB was not embryotoxic or teratogenic in rabbits at 300 ppm. More information on how this MRL was calculated is presented in Appendix A of this profile.

- An MRL of 0.2 ppm has been derived for intermediate-duration inhalation exposure (15 to 364 days) to 1,4-dichlorobenzene.

This MRL was calculated using a NOAEL of 96 ppm, based on the absence of liver effects in rats (Hollingsworth et al. 1956). The concentration of 96 ppm was converted to 20 ppm, incorporating adjustments for intermittent exposure (7 hours a day, 5 days a week). The NOAEL was further adjusted for Human Equivalent Concentration (NOAEL$_{,,}$) using Equation 4-48a of EPA (1994k) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). Cloudy swelling and granular degeneration of the liver parenchymal cells from the central zone were reported at concentrations of 158 ppm or greater. More information on how this MRL was calculated is presented in Appendix A of this profile.

The MRL was based on liver toxicity rather than kidney toxicity because the effects of 1,4-dichlorobenzene on the kidneys of male rats are associated with the occurrence of hyaline droplets from $\alpha_{2\mu}$-globulin and are not applicable to humans (EPA 1991i).

- An MRL of 0.1 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to 1,4-dichlorobenzene.

This MRL was calculated using a NOAEL of 75 ppm, based on the absence of liver effects in rats (Riley et al. 1980). The NOAEL of 75 ppm was converted to 11 ppm after incorporating adjustments for intermittent exposure (5 hours per day, 5 days per week). The NOAEL was further adjusted for Human Equivalent Concentration ($NOAEL_{HEC}$) using Equation 4-48a of EPA (199413) and by applying an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). Groups of young rats (90-l 10 g body weight) were exposed whole-body to 0 (air control), 75, or 500 ppm p-DCB 5 hours a day, 5 days a week for 76 weeks. Interim sacrifices were conducted at weeks 26, 52, and 76. After exposure terminated, groups of rats were kept until natural death or week 112. End points examined include clinical or behavioral abnormalities, body and organ weights (liver, kidney, adrenal, spleen, gonads, heart, lung, brain, and pituitary), food and water consumption, histopathology (adrenal, aorta, bladder, brain, bone marrow, cecum, colon, cervix, duodenum, epididymis, esophagus, eyes, heart, ileum, jejunum, kidneys, larynx, liver, lungs, lymph nodes, mammary gland, nasal sinuses ovaries, pancreas, pituitary, prostate, salivary glands, sciatic nerve, seminal vesicle, spinal cord, spleen, stomach, testes, trachea, thymus, thyroid, uterus, voluntary muscle, Zymbal's gland and Harderian gland), blood chemistry, urinalysis and hematology. Exposure to p-DCB had no effect on survival rate, body weight, food intake, or water consumption. No significant toxicological effects were noted on the respiratory, cardiovascular, hepatic, or renal systems at 75 ppm. There was a slight increase in lung weight only at termination (week 122) at 500 ppm in males and females, but no histopathological effects in the nasal sinuses, trachea, or lungs. Both sexes showed a significant increase in heart weight at termination, but no histopathological effects in the heart or aorta. No effects were observed in the gastrointestinal tract or in skeletal muscle. Although some changes in blood chemistry and hematology parameters were seen, there was no evidence of dose-related patterns. Liver weights were increased at 500 ppm (except in females at week 76), but there were no histological changes or changes in enzyme activity that would indicate liver damage. There was also no increase in the activity of hepatic aminopyrine demethylase. Kidney weights were increased at 500 ppm in males, but there was no evidence of histologic changes. There were no

treatment-related effects on the thyroid, pituitary, adrenals, or the eyes. More information on how this MRL was calculated is presented in Appendix A of this profile.

Oral MRLs.

An acute-duration MRL was not derived for oral exposure to 1,4-dichlorobenzene due to the lack of adequate data in humans or animals for identifying reliable NOAEL or LOAEL values.

- An MRL of 0.4 mg/kg/day has been derived for intermediate-duration (15 to 364 days) exposure to 1,4-dichlorobenzene.

This MRL was calculated using a LOAEL of 188 mg/kg/day, based on the presence of minimal liver effects (increased liver weights) in rats (Hollingsworth et al. 1956). This dose was converted to 134 mg/kg/day, incorporating adjustments for exposure for 5 days a week and an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans and 10 for human variability). In this study, hepatic necrosis and slight cirrhosis were seen at dose levels of 376 mg/kg/day or greater. Increased liver weight was also reported at doses of 188 mg/kg/day and greater and was classified as a minimal LOAEL for MRL purposes. More information on how this MRL was calculated is presented in Appendix A of this profile.

A chronic-duration oral MRL was not derived for oral exposure to 1,4-dichlorobenzene because the data were not considered to be suitable. Hepatocellular degeneration was observed in mice at a LOAEL of 300 mg/kg/day and was accompanied by hepatocellular carcinomas and hepatoblastomas (NTP 1987). There was no NOAEL in this study. The lack of the NOAEL and the occurrence of tumors at the LOAEL concentration indicate that this study is not suitable for an MRL determination.

Death. There are some data to suggest that lethality may be a public health concern for persons exposed for prolonged periods of time to high levels of 1,4-dichlorobenzene in confined areas (e.g., in homes). The only available information related to the death of humans exposed to 1,4-dichlorobenzene is a case study of a 60-year-old man and his wife who both died of liver ailments after the air in their home had been found to contain increased air concentrations of 1,4-dichlorobenzene (described as “saturated”) for 3-4 months (Cotter 1953). However, the exact air concentration of 1,4-dichlorobenzene was not measured or reported, nor was the existence or nature of other possible factors contributing to their deaths (e.g., pattern of alcohol

consumption, exposure to other chemicals, or pre-existing medical conditions). By comparison, no mice died when exposed to 320 ppm for 5 days, while 2 of 6 died at 640 ppm (Anderson and Hodge 1976). Increased mortality was also noted in one intermediate-duration study when rats, guinea pigs, and rabbits were exposed to 798 ppm for 9-12 weeks (Hollingsworth et al. 1956). These data suggest that if humans are as sensitive to the effects of inhaled 1,4-dichlorobenzene as these laboratory animals, an increased probability of death may be expected at exposures of >500 ppm. There is insufficient data available, however, to determine if humans are more or less sensitive to the 1,4-dichlorobenzene than are laboratory animals. It is unlikely that levels of 1,4-dichlorobenzene in the air of the general environment or in the vicinity of hazardous waste sites would be high enough to cause mortality.

There are several studies available on the lethality of 1,4-dichlorobenzene via the oral route in laboratory animals. Acute-duration oral studies indicate no deaths occurred in rats, guinea pigs, or mice at doses <l,000 mg/kg/day. Acute oral LD_{100} (lethal dose, 100% kill) values in rats and guinea pigs have been reported as 4,000 and 2,800 mg/kg/day, respectively (Hollingsworth et al. 1956); 3,800 mg/kg/day has been reported as the acute oral LD,, in rats (Gaines and Linder 1986). In contrast, a study by Allis et al. (1992) reported that rats receiving a single dose of 1,4-dichlorobenzene as high as 27,900 mg/kg in corn oil via gavage suffered no subsequent mortality. These data should be viewed cautiously because there was only one animal per dose group and the animals were sacrificed within 24 hours after dosing. A significantly higher mortality rate may have been observed in these rats had the animals been allowed to live longer before termination. In 14-day studies, doses of 600 mg/kg/day failed to elicit death (Carlson and Tardiff 1976), while 4 of 5 female rats that received 1,4-dichlorobenzene at 1,000 mg/kg/day died (NTP 1987). High mortality was also seen in male rats that received 1,4-dichlorobenzene at 300 mg/kg/day for 2 years (NTP 1987). Mice tested in the NTP (1987) study seemed far less susceptible than rats to the lethal effects of 1.4-dichlorobenzene.

No reports of human death after ingesting 1,4-dichlorobenzene have been reported; however, there is some concern that ingestion of 1,4-dichlorobenzene could result in human mortality based on two factors. First, 1,4-dichlorobenzene is used in many homes in the form of consumer products such as mothballs and toilet bowl deodorant blocks. Because of its availability in the form of mothballs and its pleasant taste, 1,4-dichlorobenzene can be accidentally ingested by young children. Secondly, a 19-year-old woman ingested 4-5 pellets of 1,4-dichlorobenzene daily for about 2.5 years (Frank and Cohen 1961); in another case a 21-year-old woman consumed one or two 1,4-dichlorobenzene toilet bowl deodorizer blocks per

week throughout her pregnancy (Campbell and Davidson 1970). Thus, based on its availability and potential organoleptic appeal, it is possible that sufficient amounts of 1,4-dichlorobenzene could be consumed to pose a threat to human life. However, no reports of death resulting from accidental or intentional ingestion of 1,4-dichlorobenzene have been located. Based on its minimal solubility in water, it is unlikely that levels of this chemical in drinking water at any location, even a hazardous waste site, would be high enough to cause lethality.

Systemic Effects.

Respiratory Effects. Respiratory effects associated with inhalation of 1,4-dichlorobenzene have been reported in two human case studies and three animal studies. In one human case study, a 53-year-old woman developed pulmonary granulomatosis as a result of inhaling 1,4-dichlorobenzene crystals in her home for 12-15 years (Weller and Crellin 1953). These crystals apparently lodged and accumulated in her lungs for some period of time, resulting in fibrosis, thickening of the alveolar and arterial walls, and infiltration by large numbers of lymphocytes and mononuclear phagocytes. These effects were apparently related to the physical characteristics of the 1,4-dichlorobenzene crystals that this patient had inhaled. Inhalation of large amounts of particulate matter of any composition is generally damaging to the lung and usually associated with fibrotic changes. Although this case study is most appropriately viewed as an unusual and isolated incident, it is important as a demonstration that chemical toxicity is not necessarily the only concern for a product that is available in crystalline or powdered form. In another study involving occupationally exposed men, 1,4-dichlorobenzene resulted in local irritant effects in the nose at concentrations of 80-160 ppm (Hollingsworth et al. 1956). An apparent tolerance threshold of >160 ppm was also established for this population of men.

Respiratory effects have also been reported in animal studies using 1,4-dichlorobenzene vapor. After 16 days of exposure to 1,4-dichlorobenzene at 173 ppm, slight changes (interstitial edema and congestion and alveolar hemorrhage) were reported in the lungs of male rats, female guinea pigs, and a female rabbit. Congestion and emphysema were also reported in the lungs of rabbits exposed to 1,4-dichlorobenzene at 798 ppm for 12 weeks (Hollingsworth et al. 1956). In rats exposed chronically to 1,4-dichlorobenzene concentrations up to 499 ppm, small increases in lung weights were noted, with no histopathological changes noted in the lungs, trachea, or larynx. These findings suggest that respiratory effects are a possible concern for humans exposed to 1,4-dichlorobenzene via inhalation. However, relatively high

concentrations of inhaled 1,4-dichlorobenzene are apparently needed to elicit any significant changes, and it is unlikely that levels of 1,4-dichlorobenzene in the air of the general environment or in the vicinity of hazardous sites would be high enough to cause respiratory effects.

Respiratory effects after oral exposure to 1,4-dichlorobenzene in humans have not been reported. Rats exposed to ≥1,200 mg/kg/day 1,4-dichlorobenzene for 13 weeks exhibited necrosis of the nasal turbinates, yet no such effects were noted in mice exposed to similar oral concentrations (NTP 1987). The mechanism related to this effect is not readily apparent. No effect on the respiratory system was noted in one study of chronic duration in both rats and mice exposed to ≤600 mg/kg/day for 2 years (NTP 1987).

Cardiovascular Effects. No reports of cardiovascular alterations after inhalation or oral exposure to 1,4-dichlorobenzene in humans have been reported.

Acute exposures in rats (Hodge et al. 1977) up to 508 ppm for 10 days produced no cardiovascular effects. Other acute- or intermediate-duration exposures using lower doses confirmed a no-effect scenario on the cardiovascular system. One chronic-duration study in which rats were exposed to 490-499 ppm of 1,4-dichlorobenzene for 112 weeks, did produce a significant increase in absolute heart weight, yet no abnormal histopathology was noted. No such effect was observed in rats exposed to 72 ppm for similar durations of exposure. The significance of this increased heart weight is not known. Oral exposure of 1,4-dichlorobenzene in rats (1,500 mg/kg/day) and mice (1,800 mg/kg/day) by gavage for 13 weeks failed to produce any observable cardiovascular effects. Rats and mice exposed chronically to concentrations up to 600 mg/kg/day via gavage for 2 years also failed to produce any observable cardiovascular effects. It appears that the cardiovascular system is not a target organ for 1,4-dichlorobenzene after inhalation or oral exposures.

Gastrointestinal Effects. Limited information is available for the gastrointestinal effects of 1,4-dichlorobenzene in humans after inhalation exposure. Two reports provide rather vague and non-specific information on gastrointestinal disturbances, such as increased frequency of bowel movements and blood in the gastrointestinal tract, after inhalation exposure to unknown concentrations of 1,4-dichlorobenzene (Cotter 1953). Blood in the gastrointestinal tract was reported in this study; however, the presence of blood was likely not due to a direct effect of 1,4-dichlorobenzene, but rather due to the presence of ruptured esophageal varices that formed in response to liver cirrhosis. The human data available are not sufficient

to draw any conclusions about the gastrointestinal toxicity of 1,4-dichlorobenzene either by inhalation or oral routes of exposure. No gastrointestinal effects were noted in rats exposed to 1,4-dichlorobenzene concentrations of 490-499 ppm for 76 weeks. It would appear more likely that gastrointestinal effects would be more frequently observed after oral exposure; however, only one laboratory animal study found gastrointestinal effects associated with oral exposure to 1,4-dichlorobenzene (NTP 1987). In that study, 1,200 mg/kg/day via gavage for 13 weeks resulted in epithelial necrosis and villar bridging of the small intestine mucosa. Lower-concentration exposures did not produce any effects on the gastrointestinal system in rats; oral exposures as high as 1,800 mg/kg/day for 13 weeks in mice also failed to produce any gastrointestinal effects. A 2-year chronic-duration study in both rats and mice exposed to 1600 mg/kg/day by gavage also did not produce any discernible gastrointestinal effects (NTP 1987). The laboratory animal data suggest that the gastrointestinal tract is relatively resistant to any toxicological effects that may be produced by exposure to 1,4-dichlorobenzene. Rats appear to be somewhat more susceptible to oral toxicity of 1,4-dichlorobenzene than mice.

Hematological Effects. Limited information is available for the hematological effects of 1,4-dichlorobenzene in humans after inhalation exposure. Two reports provide rather vague and non-specific information on hematological disturbances (anemia), with no exposure concentrations or information on other factors that could produce a similar finding (Cotter 1953), but the disturbances are likely related to the formation of and bleeding from esophageal varices that occur secondary to 1,4-dichlorobenzene-induced liver cirrhosis. However, no adverse hematological alterations were noted in an occupational study of men exposed to 10-550 ppm of 1,4-dichlorobenzene for 8 months to 25 years (Hollingsworth et al. 1956), indicating that in healthy men, 1,4-dichlorobenzene appears to have little toxicological effect. Overall, there are insufficient human data available to draw any conclusions about the hematological toxicity of 1,4-dichlorobenzene by the inhalation route of exposure. No hematological alterations were reported in rats exposed to 1,4-dichlorobenzene concentrations as high as 499 ppm for as long as 76 weeks (Riley et al. 1980).

Hematological effects resulting from oral exposure to 1,4-dichlorobenzene have been reported in one human case study and in several studies in rodents. Severe anemia was reported to have occurred in a 21-year-old pregnant woman who had consumed l-2 blocks of 1,4-dichlorobenzene air freshener per week throughout pregnancy. Her condition was described as hypochromic (pale blood due to reduced hemoglobin content), microcytic (smaller and rounder red blood cells) anemia with excessive

polychromasia, marginal nuclear hypersegmentation of the neutrophils, and the presence of Heinz bodies in her red blood cells (Campbell and Davidson 1970). Her infant was born with no hematological abnormalities and the woman's own hematological condition gradually reversed itself after she discontinued consumption of 1,4-dicholorobenzene. Acute hemolytic anemia and methemoglobinemia were reported to have occurred in a 3-year-old boy who had played with, and possibly eaten, some 1,4-dichlorobenzene moth crystals (Hallowell 1959). The results of both investigations could be explained by the inhibition of G6PD in red blood cells by oxidant metabolites of 1,4-dichlorobenzene with subsequent Heinz body formation, methemaglobinemia, and hemolysis (Trieff et al. 1993).

Male Fischer 344 rats were administered doses of up to 2,790 mg/kg body weight of 1,4-dichlorobenzene once via corn oil gavage. No hematological alterations were noted in any of the treated animals 24 hours after dosing (Allis et al. 1992). Rats administered 1,4-dichlorobenzene doses of 75-600 mg/kg/day by gavage in corn oil for 13 weeks did not experience any changes in hematologic parameters (Bornhard et al. 1988), neither did rats in a study by Hollingsworth et al. (1956)in which rats received 376-500 mg/kg/day for 28-192 days. In contrast, decreased hematocrit levels, red blood cell counts, and hemoglobin concentrations were measured in male rats that received 1,4-dichlorobenzene for 13 weeks at 300 mg/kg/day and above (NTP 1987). However, these effects were not seen in male rats that received 1,4-dichlorobenzene at 300 mg/kg/day for 2 years (NTP 1987). No hematologic effects were seen in female rats at any level of 1,4-dichlorobenzene tested (up to 600 mg/kg/day for 2 years) in the same set of studies. In the NTP (1987) study, mice dosed with concentrations up to 900 mg/kg/day for 13 weeks produced no hematological alterations, while in a second study by NTP (1987), mice dosed with 600-1,800 mg/kg/day for 13 weeks produced lymphopenia and neutropenia (no red blood cell anomalies). The human and laboratory animal data suggest that the hematological system is susceptible to the effects of 1,4-dichlorobenzene. It is not known, however, if this is a result of a direct action on the red and white blood cells, or an effect on the red and white cell precursor cells of the bone marrow (as is the case with benzene toxicosis in humans). It is assumed that 1,4-dichlorobenzene is the chemical responsible for this alteration; however, interaction with the primary metabolite on the hematopoietic system can not be ruled out from this set of data. The inhibition of G6PD in red blood cells by oxidant metabolites of 1,4-dichloro-benzene with subsequent Heinz body formation, methemaglobinemia, and hemolysis could be responsible for this effect (Trieff et al. 1993).

The effects of 1,4-dichlorobenzene ingestion on hematological parameters reported in both human and animal studies indicate that this is an area of potential concern for humans exposed to 1,4-dichlorobenzene. Possible effects in humans have been associated with red blood cells anomalies. Because of sex and species differences seen in animal studies (i.e., effects on red blood cells in rats and effects on white blood cells in mice), the total spectrum of concern for exposed humans is currently not clear. However, it is unlikely that levels of 1,4-dichlorobenzene in the drinking water of any location would be high enough to cause hematological effects.

Musculoskeletal Effects. There were no reports of human exposure that resulted in musculoskeletal effects. The few reports that examined the musculoskeletal system after exposure to 1,4-dichlorobenzene in laboratory animals failed to elicit detectable changes in this system.

Hepatic Effects. Liver effects reported in case studies in humans exposed to 1,4-dichlorobenzene via inhalation have included jaundice, cirrhosis, and atrophy (Cotter 1953). Estimates of exposure duration ranged from 1 to 18 months; however, quantitative data on 1,4-dichlorobenzene levels were not available. One report was located that described a 3-year-old boy who may have ingested 1,4-dichlorobenzene crystals. Jaundice was reported, indicating that liver function was in some way compromised, although no further details were reported. No dermal exposures to 1,4-dichlorobenzene in humans were reported. The lack of reliable information regarding human exposures to 1,4-dichlorobenzene by all three routes of exposure makes it difficult to draw any helpful conclusions about the toxicity of 1,4-dichlorobenzene in humans.

Hepatic effects have been demonstrated in several animal studies conducted via inhalation and oral exposure with durations ranging from 3 days to 2 years. Observed effects have ranged from enzyme changes and porphyria to liver degeneration and necrosis.

Hepatic effects reported in inhalation studies have not been consistent. Acute-duration studies in rats and rabbits exposed to concentrations as high as 500-800 ppm failed to produce detectable hepatic effects (Hayes et al. 1985; Hodge et al. 1977). In inhalation studies of 5-7 months duration, exposure of rats and guinea pigs to 158-341 ppm resulted in cloudy swelling, granular degeneration, slight cirrhosis, focal necrosis, and fatty degeneration of the liver (Hollingsworth et al. 1956). Relative liver weights were also increased in rats exposed to 173 ppm and above. In a more recent study, however, a 1.5-year exposure of

rats to 1,4-dichlorobenzene at 500 ppm resulted in increased liver weight but no other liver pathology, including no increases in serum transaminase activity (Riley et al. 1980).

In oral studies, severe cases of porphyria (an indication of liver damage as evidenced by increased urinary excretion of porphyrins and high hepatic levels of porphyrins) were induced in male rats that received 1,4-dichlorobenzene during a short-term, high-level dosage regimen (770 mg/kg/day for 5 days) (Rimington and Ziegler 1963). However, only slight increases in liver porphyrins (but not in urinary excretion of porphyrins) were seen in female rats that received 1,4-dichlorobenzene at 50 mg/kg/day and above for 120 days (Carlson 1977). It is not clear if the observed differences are due to the dosing regimens or to sex-related differences in sensitivity to 1,4-dichlorobenzene.

Oral exposure to 1,4-dichlorobenzene has been shown to result in changes in the activities of certain hepatic enzymes in rats, including increases in the activity of δ-ALA synthetase at a 1,4-dichlorobenzene level of 250 mg/kg/day for up to 3 days (Ariyoshi et al. 1975); increases in the activities of glucuronyl transferase, benzpyrene hydroxylase, and the enzyme system involved in EPN detoxification to p-nitrophenol at 1,4-dichlorobenzene levels of 20 mg/kg/day and above for 14 days (Carlson and Tardiff 1976); increases in benzpyrene hydroxylase, and EPN detoxification activities at 1,4-dichlorobenzene levels of 20 mg/kg/day and above for 90 days, and increases in azoreductase levels at 10 mg/kg/day and above for 90 days (Carlson and Tardiff 1976). There was also no effect observed on serum levels of ALT and AST in male Fischer 344 rats given one dose as high as 2,790 mg/kg of 1,4-dichlorobenzene per body weight by corn oil gavage. No consistent pattern of change was found for indicators of hepatobiliary damage, serum cholesterol, serum alkaline phosphatase, and total bilirubin (Allis et al. 1992).

These findings are viewed as an important component of the hepatotoxic potential of 1,4-dichlorobenzene. Even though elevations in levels of hepatic enzymes are not in themselves always considered to be of major toxicological concern, the fact that these changes can occur even at 1,4-dichlorobenzene levels as low as 10 or 20 mg/kg/day in 14- and 90-day exposure regimens indicates that the liver is sensitive to 1,4-dichlorobenzene at exposure levels far below those that evoke severe histopathological damage. It is also important to note that a true NOAEL for hepatic effects has not been identified since effects on hepatic enzymes have been found at the lowest levels of 1,4-dichlorobenzene tested and the potential long-term consequences of these effects on enzyme activities and their relationship to overt hepatic lesions are not clearly understood.

Histopathologic lesions of the liver have been demonstrated in several oral studies in rodents dosed at higher levels of 1,4-dichlorobenzene. Cloudy swelling and centrilobular necrosis were observed in the livers of rats that received 1,4-dichlorobenzene at 500 mg/kg/day for 4 weeks (Hollingsworth et al. 1956). Thirteen-week studies have resulted in degeneration and necrosis of hepatocytes in rats that received doses of 1,200 mg/kg/day and above; and in mice, hepatocellular degeneration was observed at 600 mg/kg/day and above and hepatocellular cytomegaly at 675 mg/kg/day and above (NTP 1987). Focal necrosis and slight cirrhosis were reported in the livers of rats dosed at 376 mg/kg/day for about 6 months (Hollingsworth et al. 1956). In 2-year studies, mice that received 1,4-dichlorobenzene at 300 mg/kg/day and above, had increased incidences of cytomegaly, karyomegaly, hepatocellular degeneration, and singlecell necrosis (NTP 1987). No hepatic effects, however, were found in a 2-year study in rats (males received up to 300 mg/kg/day; females received up to 600 mg/kg/day) (NTP 1987).

The results of the available studies generally indicate that mice are somewhat more sensitive than rats to the more severe histopathological effects of 1,4-dichlorobenzene on the liver. However, the liver is clearly a target organ in both species.

Oral exposure to 1,4-dichlorobenzene in rats and mice has been demonstrated to cause a cellular proliferation response in the livers of these animals. 1,4-Dichlorobenzene is not known to be reactive with DNA (i.e., not genotoxic as determined by standard assays); however, it has been reported to induce liver tumors in mice (NTP 1987). Studies by Eldridge et al. (1992) demonstrated sharp increases in cell proliferation in mouse livers beginning 24 hours after a single dose of 600 mg/kg/day of 1,4-dichlorobenzene in oil. There was also an increase in liver weight without increase in liver-associated plasma enzymes, indicating a lack of cytotoxicity to the hepatocytes. Significant dose-related increases in microsomal cytochrome P-450 content were observed in rats given 150 and 300 mg/kg 1,4-dichlorobenzene for 1 week, with a significant dose-related induction of microsomal 7-pentoxyresorufin O-dependentylase activity observed in rats given 75-300 mg/kg 1,4-dichlorobenzene. The BrdU hepatocyte labeling index values in male F344 rats given 25, 75, 150, and 300 mg/kg/day 1,4-dichlorobenzene only increased in animals given 300 mg/kg 1,4-dichlorobenzene (225% of controls) for 1 week but not for 4 or 13 weeks (Lake et al. 1997). A similar study was performed in mice (Umemura et al. 1996. BrdU hepatocyte labeling index values were significantly increased in mice given 300 and 600 mg/kg 1,4-dichlorobenzene for 1 (475% and 1,175% of controls, respectively) and 4 weeks (420 and 395% of controls, respectively) (Lake et al. 1997). From the sum of these data it is hypothesized that this early mitogenic stimulation of

cell proliferation after oral exposure to 1,4-dichlorobenzene may be, at least in part, the mechanism behind the tumor formations found in mice in the NTP (1987) study. This increased cellular proliferation response may provide a selective growth advantage for neoplastic cell in the mouse liver after long-term treatments, which ultimately results in hepatic neoplasms. The implications for human cancer health risks are unknown at this point; however, it is unlikely that levels of 1,4-dichlorobenzene in the drinking water would be high enough to cause proliferative and mitogenic hepatic effects observed in rats and mice, based on the potential human exposure data presented in Chapter 5 of this profile.

Based on the results of studies in humans and animals, humans exposed to 1,4-dichlorobenzene could experience a variety of hepatic effects ranging from increased hepatic enzyme activity at low levels of exposure to severe histopathological effects resulting from high levels of exposure. It is unlikely, based on the NOAELs and LOAELs demonstrated in laboratory animal studies and human case reports, that the reported levels of 1,4-dichlorobenzene in the air of the general environment, or in the vicinity of hazardous waste sites, or in the drinking water of any location (measured at concentrations as low as parts per billion) would be high enough to cause hepatic or other toxicological effects in humans. More information on the amounts and presence of 1,4-dichlorobenzene in the environment can be found in Chapter 5 of this profile.

Endocrine Effects. No studies were identified that described endocrine organ effects in humans after inhalation or oral exposure to 1,4-dichlorobenzene.

No endocrine organ effects were noted in rats exposed to 490-499 ppm 1,4-dichlorobenzene for 76 weeks (Riley et al. 1980). No endocrine effects were noted in rats dosed with 1,500 mg/kg/day of 1,4-dichlorobenzene in oil for 13 weeks (NTP 1987). However, rats dosed with 150 or 300 mg/kg/day (males) or 300-600 mg/kg/day (females) 1,4-dichlorobenzene in oil for 103 weeks produced an increased incidence of parathyroid hyperplasia in males only; females, given higher doses than the males, were unaffected. The dosing of male and female mice with 300 and 600 mg/kg/day in oil for 103 weeks produced thyroid follicular cell hyperplasia in males only; females were unaffected. Adrenal medullary hyperplasia and focal hyperplasia of the adrenal gland capsule were also observed in these male mice (NTP 1987). Clearly, there is a sex-related difference in toxicity relating to endocrine organ toxicity; it may be related to the production of testosterone in male rats and mice. Chemical disruption of endocrine function has been described for a number of other chemicals; however, the significance to human exposure to these chemicals (including 1,4-dichlorobenzene) is not known.

Renal Effects. Renal effects have not been reported in humans exposed to 1,4-dichlorobenzene by any route, but renal effects have been reported in inhalation and oral studies in animals.

Several studies have identified no-effect levels after inhalation exposure in laboratory animals (Hayes et al. 1985; Hodge et al. 1977). In inhalation studies, renal effects have been limited to increased kidney weights in male, but not female, rats exposed to 158 or 341 ppm for 5-7 months (Hollingsworth et al. 1956).

Severe renal changes have been reported in oral studies using rats; some of these effects have been seen only in male Fischer 344 rats as opposed to female rats or mice of either sex. In 13-week studies in rats, histologic changes, including tubular degeneration, were seen in the kidneys of all males dosed with 1,4-dichlorobenzene at 300-l ,500 mg/kg/day (NTP 1987). In a follow-up 13-week study at lower doses, however, only slight to moderate changes in the tubules were seen in males at 300-600 mg/kg/day. Studies by Eldridge et al. (1992) demonstrated that $B6C3F_1$ mice dosed with 300 or 600 mg/kg/day of 1,4-dichlorobenzene for 4 days had no altered kidney weights or cell proliferation rates as measured by BrdU-labeling of the cells. Male rats dosed with 150 or 300 mg/kg/day for 4 days showed marked increases in both kidney weight and cell proliferation, while female rats dosed with 300 or 600 mg/kg/day mimicked the results found in both male and female mice. Cell proliferation in the kidneys of male rats was mainly limited to the proximal tubules, and to a lesser extent the proximal straight tubules. In a follow-up study, male F344 rats given BrdU in addition to 0 (corn oil control), 25, 75, 150, and 300 mg/kg/day 1,4-dichlorobenzene (n=6-8/group/time) and male $B6C3F_l$ mice given 0 (corn oil control), 300, and 600 mg/kg/day 1,4-dichlorobenzene (n=6-8/group/time) by daily oral gavage 5 days per week for 1,4, and 13 weeks showed significant increases in rat renal Pl/P2 proximal tubule cell labeling index values at all time points. Significant increases were seen at 75 mg/kg 1,4-dichlorobenzene at 4 weeks (250% of controls); 150 mg/kg 1,4-dichlorobenzene at 4 and 13 weeks (400% and 440% of controls, respectively); and 300 mg/kg 1,4-dichlorobenzene at 1,4, and 13 weeks (170%, 475%, and 775% of controls, respectively). A significant increase in rat P3 renal proximal tubule cell labeling index values was observed in 300 mg/kg 1,4-dichlorobenzene group rats at weeks 4 (185% of controls) and 13 (485% of controls). In contrast, some reduction in rat P3 renal proximal tubule cell labeling index values was observed in 75-300 mg/kg 1,4-dichlorobenzene group rats at 1 week. In contrast, 1,4-dichlorobenzene treatment produced little effect on mouse renal P1/P2 proximal tubule cell labeling index values at all time points. No significant increase was seen in 300 or 600 mg/kg 1,4-dichlorobenzene groups for 1 and 13 weeks, but significant increases were seen at 4 weeks (205% and 170% of controls, respectively). Neither 300 nor 600 mg/kg

1,4-dichlorobenzene for 1,4, or 13 weeks had much effect on mouse P3 renal proximal tubule cell labeling index values (Lake et al. 1997). These data suggest that male rats are more sensitive to the renal effects of 1,4-dichlorobenzene than mice and that cell proliferation in these male rats may play a role in the development of tubular cell adenocarcinomas of the kidneys (see the discussion on cell proliferation and carcinogenesis in Hepatic Effects, above) found in a chronic-duration study (NTP 1987).

Administration of 1,4-dichlorobenzene by gavage to certain strains of rats under a wide variety of acuteand intermediate-duration dosage regimens has resulted in an increase in renal hyaline droplet formation in males, but not females (Bornhard et al. 1988; Charbonneau et al. 1987, 1989a, 1989b). Renal cell proliferation was also increased as indicated by ^{3}H-thymidine incorporation into renal DNA. The ^{14}C from radiolabeled 1,4-dichlorobenzene was reversibly bound to the renal protein $\alpha_{2\mu}$-globulin in the hyalin droplets. This particular protein is produced in large amounts by male rats, accounting for 26% of their total urinary output, but not in human males. A structurally related protein has been identified in human males, but that protein has not been found to bind 1,4-dichlorobenzene and is present at <1% of the amount measured in male rats (Olson et al. 1990). This protein is only produced in minimal quantities by females of any species or the males of other laboratory species, including mice (EPA 1991i). Thus, men are probably not at risk for the type of nephropathy induced by 1,4-dichlorobenzene in male rats.

Renal effects have been observed in both male and female rats in a chronic-duration oral study. Male Fischer 344 rats exposed to 1,4-dichlorobenzene at 150 and 300 mg/kg/day for 2 years exhibited nephropathy, epithelial hyperplasia of the renal pelvis, mineralization of the collecting tubules in the renal medulla, and focal hyperplasia of the tubular epithelium. Each of these effects was associated with hyalin droplet formation. There were also increased incidences of nephropathy in female Fischer 344 rats dosed with 1,4-dichlorobenzene at 300 and 600 mg/kg/day. Histopathologically, the nephropathy was characterized by degeneration and regeneration of the tubular epithelium, tubular dilatation with attenuation and atrophy of the epithelium, granular casts in the tubules of the outer stripe of the medulla, thickening of the basement membranes, and minimal accumulation of interstitial collagen (NTP 1987). In mice dosed at 300 and 600 mg/kg/day, there was also an increased incidence of nephropathy (consisting primarily of degeneration of the cortical tubular epithelium with thickening of the tubular and glomerular basement membranes and increased interstitial collagen in male mice, and renal tubular regeneration in female mice).

These observations of renal effects in female rats and in mice of both sexes are important because they provide evidence that renal lesions in response to 1,bdichlorobenzene exposure are not limited to male rats and do not require the presence of high levels of the renal protein of $\alpha_{2\mu}$-globulin. Therefore, although humans may not be at risk for certain 1,4-dichlorobenzene-induced renal lesions (renal hyaline droplet nephropathy), they are possibly at risk for others. However, it is unlikely that levels of 1,4-dichlorobenzene in the air of the general environment, or in the vicinity of hazardous waste sites, or in the drinking water of any location would be high enough to cause renal effects.

Dermal Effects. Dermal effects have been reported in humans exposed to 1,4-dichlorobenzene via inhalation or ingestion. In a study of 58 men who had been occupationally exposed to 1,4-dichlorobenzene for 8 months to 25 years, painful irritation of the nose and eyes was reported to have occurred at 1,4-dichlorobenzene levels of 80-160 ppm, yet no cutaneous effects were noted. Above 160 ppm, the air was considered unbreathable by unacclimatized persons (Hollingsworth et al. 1956). Petechiae, purpura, and swelling of the hands and feet were reported to have occurred in a 69-year-old man who had been exposed to 1,4-dichlorobenzene for about 3 weeks in his home (Nalbandian and Pearce 1965). Well demarcated areas of increased pigmentation developed in a 19-year-old black woman who had eaten four to five 1,4-dichlorobenzene moth pellets daily for the previous 2.5 years (Frank and Cohen 1961). Hollingsworth et al. (1956) reported a burning sensation occurring in men that placed solid 1,4-dichloro-benzene in close contact with the skin. Although there is no clear pattern to these observations, both irritation and sensitization reactions may potentially result from human inhalation or oral exposure to 1,4-dichlorobenzene. There are no data related to dermal effects resulting specifically from dermal exposure to 1,4-dichlorobenzene in humans.

Few laboratory animal data are available that describe the dermal affects related to inhalation, oral, or dermal exposure to 1,4-dichlorobenzene. Fischer 344 rats and B6C3F_1 mice exposed to concentrations up to 1,500 mg/kg/day and 1,800 mg/kg/day, respectively, for 13 weeks produced no dermal effects (NTP 1987). In rats exposed to 1,4-dichlorobenzene at 150-600 mg/kg/day and in mice exposed to 300 and 600 mg/kg/day in oil for 2 years no dermatological effects were produced.

Ocular Effects. No ocular effects have been reported in humans exposed to 1,4-dichlorobenzene by any route, including in the 58 men who had been occupationally exposed for 8 months to 25 years and occasionally examined for ocular effects (Hollingsworth et al. 1956). Ocular effects described as

reversible, nonspecific eye ground changes (changes in the fundus or back of the eye) were seen in rabbits exposed to 1,4-dichlorobenzene at 798 ppm for 12 weeks (Hollingsworth et al. 1956). In the same study, no changes in lens morphology and opacity were observed in rats and guinea pigs exposed to 1,4-dichlorobenzene. Rats exposed to 1,4-dichlorobenzene at doses up to 499 ppm for 76 weeks also failed to produce an adverse ocular response. These few findings do not support a clear concern for potential ocular effects in humans exposed to 1,4-dichlorobenzene in any environment. However, no studies were located that directly dosed 1,4-dichlorobenzene onto the surface of the eye in either humans or animals. Organic compounds with similar physicochemical properties and structure have been identified as ocular irritants when dosed in this fashion. It would, therefore, be premature to assume that 1,4-dichlorobenzene is not an ocular irritant when placed on the eye in the absence of the appropriate toxicological studies.

Body Weight Effects. Unknown amounts of inhaled 1,4-dichlorobenzene have been reported to cause decreases in body weight in humans (Cotter 1953). Little more significant information was reported in these individual case studies, indicating that other factors may have resulted in the loss of body weight. The human database is insufficient to draw any substantial conclusion about 1,4-dichlorobenzene's ability to cause decreases in body weight.

Changes in body weight were not reported for the majority of laboratory animals exposed to 1,4-dichlorobenzene by inhalation, even at relatively high concentrations of 798 ppm for 5-7 months.

No studies were identified that described changes in body weight in humans after oral exposure to 1,4-dichlorobenzene.

A few laboratory animal studies examined changes in body weight. Acute exposure in rats to 600 mg/kg/day once (Eldridge et al. 1992), 250 mg/kg/day for 3 days (Ariyoshi et al. 1975), and 770 mg/kg/day for 5 days (Eldridge et al. 1992) revealed no changes in body weight. Intermediate-duration studies using similar doses have also proved to have little if any effect on body weight in rats and mice (NTP 1987). Other studies (NTP 1987) of intermediate- and chronic-durations in rats and mice showed mixed results as to whether 1,4-Dichlorobenzene actually produces discernible changes in body weight in laboratory animals.

Immunological and Lymphoreticular Effects. Little information was located on immunological effects in humans or animals exposed to 1,4-dichlorobenzene via inhalation, oral, or dermal routes. An enlarged spleen was noted in two people exposed to 1,4-dichlorobenzene (dose not reported); data on alterations in spleen weights have varied in laboratory animals exposed for different durations (Hollingsworth et al. 1956; Riley et al. 1980). Observations of blotchy skin pigmentations in a black 19-year-old woman who had eaten 4-5 pellets of 1,4-dichlorobenzene daily for 2.5 years (Frank and Cohen 1961), and the observations of purpura, petechiae, and swelling of the hands and feet of the 69-year-old man who had been exposed to 1,4-dichlorobenzene for about 3 weeks via inhalation (Nalbandian and Pearce 1965) suggest that immunological mechanisms were involved and that this is an area of potential concern for humans exposed to 1,4-Dichlorobenzene. Bone marrow hypoplasia and lymphoid depletions of the spleen were reported in one study using both rats and mice dosed with 1,200-l ,500 mg/kg/day of 1,4-dichlorobenzene for 13 weeks (NTP 1987); however, at 600 mg/kg/day for 2 years, no changes to the lymphoreticular system were noted in rats (NTP 1987). Mice still showed an increased incidence of lymph node hyperplasia. Together, these data suggest that there may be an immunological component involved in 1,4-dichlorobenzene toxicity; however, the threshold for these effects and their mechanisms is not known.

Neurological Effects. Neurological effects have been reported in humans exposed to 1,4-dichlorobenzene via inhalation. Symptoms have included dizziness, weakness, headaches, nausea, vomiting, numbness, clumsiness, a burning sensation, and speech difficulties (Cotter 1953; Miyai et al. 1988). In the recent case study of a 25-year-old woman who had been exposed to high concentrations of 1,4-dichlorobenzene in her bedroom, bedding, and clothes for 6 years, there were marked delays of certain brainwaves, as indicated by electronic testing of BAEPs, in addition to severe ataxia, speech difficulties, and weakness in her limbs (Miyai et al. 1988). Non-specific clinical neurological alterations (tremors, weakness, unconsciousness, ataxia, hyperactivity, etc.) have been reported in rats, rabbits, and guinea pigs (Hollingsworth et al. 1956; Riley et al. 1980; Rimington and Ziegler 1963; Tyl and Neeper-Bradley 1989); however, these type of effects have been reported with other volatile organic chemicals (carbon tetrachloride, chloroform, benzene) as well, indicating some neurological component to its toxicity. While there is no clear evidence of neurological effects in humans who ingested 1,4-dichlorobenzene and no information on neurological effects in animals exposed by any route, the available information on humans and laboratory animals exposed to 1,4-dichlorobenzene via inhalation strongly suggests that this is not an area of potential concern. It is not probable that the levels of 1,4-dichlorobenzene in the air of the general environment or in the vicinity of hazardous waste sites would be high enough to cause neurological effects.

Reproductive Effects. No information was located regarding the reproductive effects in humans exposed to 1,4-dichlorobenzene by any route.

From the available data on 1,4-dichlorobenzene, exposure by inhalation and oral routes appears to have little to no effect on the reproductive systems of either male or female laboratory animals. In a 2-generation study of reproductive performance using exposure concentrations of 66.3-538 ppm 1,4-dichlorobenzene, toxic effects on the liver, kidney, and body weight were noted in breeding rats (males and females) (Tyl and Neeper-Bradley 1989). The effects of exposure on litter size, weight, and survival appeared to result from the maternal toxicity of the compound rather than direct effects on reproductive processes. However, offspring were not examined for developmental or teratogenic effects. In addition, no decrease in reproductive performance (ability to impregnate females) was found in an inhalation study in which male mice were exposed to 1,4-dichlorobenzene for 5 days at levels up to 450 ppm (Anderson and Hodge 1976). No effect on testicular weight was noted in rats and guinea pigs exposed to 173 ppm 1,4-dichlorobenzene for 2 weeks (Hollingsworth et al. 1956), and no changes were noted in the reproductive organs of male and female rats exposed up to 499 ppm for 76 weeks (Riley et al. 1980).

In another study, statistically significant increases in the incidences of abnormal sperm heads and tails were seen in male rats that had received a single intraperitoneal injection of 1,4-dichlorobenzene at 800 mg/kg/day (Murthy et al. 1987). The potential effects of these abnormalities (e.g., banana- and wedge-shaped heads, twisted and curly tails) on reproductive capacity is not known, but paternal effects were not noted in the 2-generation study discussed above. The nonbiological route of administration somewhat complicates the interpretation of these results. It is not likely, based on the potential for human exposure data presented in Chapter 5, coupled with the NOAELs and LOAELs gathered from human case reports and laboratory animal studies, that the levels of 1,4-dichlorobenzene in the air of the general environment, or in the vicinity of hazardous waste sites, or in drinking water in any location would cause reproductive effects.

Developmental Effects. There is little evidence of developmental effects in the offspring of humans exposed to 1,4-dichlorobenzene via any route. Only one human case report mentions the potential developmental effects of ingesting 1,4-dichlorobenzene at 38 weeks of gestation. The mother developed hematological effects due to 1,4-dichlorobenzene consumption, but she delivered a normal 4.3-kg female infant (Campbell and Davidson 1970).

Animal studies have shown an increased incidence of retroesophageal right subclavian artery in fetuses of rabbits exposed to 1,4-dichlorobenzene via inhalation at 800 ppm on Gd 6-18 (Hayes et al. 1985), and an increased incidence in the presence of an extra rib in the fetuses of rats that received 1,4-dichlorobenzene by gavage at doses of 500 mg/kg/day and above (Giavini et al. 1986). Although neither effect was viewed as constituting a true teratogenic response by the authors, the results of these two studies suggest that 1,4-dichlorobenzene inhaled or ingested by pregnant animals can reach the developing fetus and affect its development. However, it is not likely that the levels of 1,4-dichlorobenzene in the air of the general environment, or in the vicinity of hazardous waste sites, or in drinking water in any location would be high enough to pose a risk for developmental effects in humans.

Genotoxic Effects. No studies were located regarding genotoxic effects in humans after inhalation oral, or dermal exposure to 1,4-dichlorobenzene.

Cytogenetic studies conducted using rats exposed to 1,4-dichlorobenzene via inhalation using various dosage regimens have been negative (Anderson and Richardson 1976). Similarly, no cytogenetic effects were observed in studies using mice treated with 1,4-dichlorobenzene via gavage at levels that resulted in liver toxicity and decreased survival in the test animals (NTP 1987).

However, gavage administration of a single 1,000 mg/kg/day dose of 1,4-dichlorobenzene to mice and rats resulted in an increase in DNA replication in the renal tissue of the male rats and in the hepatocytes of mice of both sexes (Steinmetz and Spanggord 1987a, 1987b). Increased ^{3}H-thymidine incorporation into renal DNA has also been demonstrated in rats dosed with 1,4-dichlorobenzene by gavage at 120 mg/kg/day for 7 days (Charbonneau et al. 1989b). These observations suggest that 1,4-dichlorobenzene promotes cell division, a finding that may help to elucidate the mechanism of carcinogenic action of 1,4-dichlorobenzene in male rat kidneys and mouse liver in the NTP (1987) bioassay. However, it is important to note that in these studies, only kidney tissue was tested in the rat for increased DNA replication, and in the mouse, only liver tissue was tested. Therefore, it is not clear whether increased cell replication also occurs in other tissue in each species or is limited to the tissues in which the carcinogenic effects occurred.

Summaries of the *in vivo* and *in vitro* studies related to the genotoxicity of 1,4-dichlorobenzene are presented in Tables 2-3 and 2-4, respectively. 1,4-Dichlorobenzene is generally nonmutagenic except in plants (see Tab 2-4) (Prasad 1970, Sarbhoy 1980; Sharma and Battacharya 1956; Srivastava 1966).

Table 2-3. Genotoxicity of 1,4-Dichlorobenzene *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Rat[a] bone marrow	Chromosomal aberrations	–	Anderson and Richardson 1976
Mouse bone marrow	Micronuclei formation	–	Shelby and Witt 1995
Mouse[b] erythrocytes	Micronucleated erythrocytes	–	NTP 1987
Rat[c] kidney cells	Unscheduled DNA synthesis Increased DNA replication	– +[d]	Steinmetz and Spanggord 1987b
Mouse[e] hepatocytes	Unscheduled DNA synthesis	–	Steinmetz and Spanggord 1987a
Rat[f] kidney cells	Increased DNA replication	+	Charbonneau et al. 1989
Mouse[g] erythrocytes of femoral bone marrow	Induction of micronuclei	–	Mohtashamipur et al. 1987
Rat[h] renal tubular cells and hepatocytes	Cumulative replicating fraction	–	Umemura et al. 1998
Mouse[h] renal tubular cells and hepatocytes	Cumulative replicating fraction	+	Umemura et al. 1998

[a] Exposed to 1,4-dichlorobenzene via inhalation for 2 hours at 299 or 682 ppm; for 5 days, 5 hours/day at 75 or 500 ppm; or for 3 months, 5 days/week, 5 hours/day at 75 or 500 ppm

[b] Exposed to 1,4-dichlorobenzene via gavage for 13 weeks, 5 days/week at 600-1800 mg/kg/day

[c] Exposed to 1,4-dichlorobenzene via gavage in corn oil at 300, 600, or 1000 mg/kg at 16 hrs before sacrifice for UDS experiment or at 96 hours before sacrifice for DNA replication experiment

[d] Results were positive for male rats only in which a significant S-phase response was induced

[e] Exposed to 1,4-dichlorobenzene via gavage in corn oil at 300, 600, or 1000 mg/kg at 16 or 48 hours before sacrifice

[f] Exposed to 1,4-dichlorobenzene via gavage in corn oil at 120 or 300 mg/kg/day for 7 days and sacrificed 24 hours after the last dose

[g] Exposed to 1,4-dichlorobenzene via two intraperitoneal injections of 355, 710, 1065, 1420 mg/kg (24 hours apart) and sacrificed 6 hours after the second injection. Males only were tested.

[h] Exposed to 1,4-dichlorobenzene via gavage for 1 week or 4 weeks at 150, 300, or 600 mg/kg/day

+ = positive result; – = negative result; DNA = deoxyribonucleic acid

Table 2-4. Genotoxicity of 1,4-Dichlorobenzene *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Mammalian systems:				
HeLa cells	Unscheduled DNA synthesis	–	–	Instituto di Ricerche Biomediche 1986a
Human lymphocytes	Unscheduled DNA synthesis	–	–	Perocco et al. 1983
Human lymphocytes	Unscheduled DNA synthesis	–	–	Instituto di Ricerche Biomediche 1987
Chinese hamster ovary cells	Chromosomal aberrations	–	–	NTP 1987
	Sister chromatid exchanges	–	–	
Chinese hamster lung cells	Gene mutation	–	–	Instituto di Ricerche Biomediche 1986b
L5178Y/TK $^{\pm}$ mouse lymphoma cells	Gene mutation	(+)	–	NTP 1987
Human hepatocytes	DNA fragmentation	-	-	Canonero et al. 1997
Rat hepatocytes	DNA fragmnetation	NS	+	Canonero et al. 1997
Plant systems:				
Root tips (16 species of dicotyledons and monocotyledons)	Chromosomal aberrations	NS	+	Sharma and Battachary 1956
Lens esculenta (L.) Moench	Mitotic abnormalities	NS	+	Sarbhoy 1980
Aspergillus nidulans	Back mutation frequency	NS	+	Prasad 1970
Tribe viceae	Chromosomal aberrations	NS	+	Srivastava 1966
Microbial systems:				
Salmonella typhimurium				Anderson 1976
TA98[a]	Gene mutation	–	–	
TA100[a]	Gene mutation	–	–	
TA1535[a]	Gene mutation	–	–	
TA1538[a]	Gene mutation	–	–	
TA98[b]	Gene mutation	–	–	
TA100[b]	Gene mutation	–	–	
TA1535[b]	Gene mutation	+	–	
TA1538[b]	Gene mutation	–	–	

Table 2-4. Genotoxicity of 1,4-Dichlorobenzene *In Vitro* (continued)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Mammalian systems:				
HeLa cells	Unscheduled DNA synthesis	–	–	Instituto di Ricerche Biomediche 1986a
Salmonella typhimurium				
TA98	Gene mutation	–	–	Shimizu et al. 1983
TA100	Gene mutation	–	–	Shimizu et al. 1983
TA1535	Gene mutation	–	–	Shimizu et al. 1983
TA1537	Gene mutation	–	–	Shimizu et al. 1983
TA1538	Gene mutation	–	–	Shimizu et al. 1983
TA98	Gene mutation	–	–	Haworth et al. 1983
TA100	Gene mutation	–	–	Haworth et al. 1983
TA1535	Gene mutation	–	–	Haworth et al. 1983
TA1537	Gene mutation	–	–	Haworth et al. 1983

[a] Exposed to 1,4-dichlorobenzene gas
[b] Exposed to 1,4-dichlorobenzene in DMSO
[c] Positive result was not reproducible in other experiments in this series

NS = not studied; – = negative results; + = positive results; (+) = weakly positive result; DNA = deoxyribonucleic acid

The results of *in vivo* systems, as discussed above, were positive only for increased DNA replication in the livers of orally exposed mice (Steinmetz and Spanggord 1987a) and in the kidneys of orally exposed rats (Charbonneau et al. 1989b; Steinmetz and Spanggord 1987b).

Cancer. No studies were located regarding cancer in humans after inhalation, oral, or dermal exposure to 1,4-dichlorobenzene.

In studies conducted using animals, evidence of carcinogenicity from 1,4-dichlorobenzene exposure is based on 2-year oral studies in mice and rats. 1,4-Dichlorobenzene was administered by gavage to male rats at doses of 150 mg/kg/day and 300 mg/kg/day, and to female rats and mice of both sexes at doses of 300 mg/kg/day and 600 mg/kg/day. There was a dose-related increase in the incidence of tubular cell adenocarcinomas of the kidneys of male rats. There were no tubular cell tumors in dosed or vehicle-control female rats. There was a marginal increase in the incidence of mononuclear cell leukemia in dosed male rats compared with either vehicle controls or historical controls (NTP 1987). Based on the finding of renal tumors in this study, 1,4-dichlorobenzene was found to be carcinogenic in male rats.

1,4-Dichlorobenzene also increased the incidences of hepatocellular carcinomas in high-dose male mice and of hepatocellular adenomas in both high- and low-dose male and in high-dose female mice. The combined increase in adenomas plus carcinomas was statistically significant at the high dose but not at the low dose. Female control mice in this bioassay had a substantially higher incidence of liver tumors than did historical controls. Hepatoblastomas (a rare form of hepatocellular carcinoma) were observed in four high-dose male mice along with other hepatocellular carcinomas, but not in vehicle controls. An increase in thyroid gland follicular cell hyperplasia was observed in dosed male mice, and there was a marginal positive trend in the incidence of follicular cell adenomas of the thyroid gland in female mice. Pheochromocytomas of the adrenal gland (benign and malignant, combined) occurred with a positive dose-related trend in male mice, and the incidence in the high-dose group was significantly greater than in vehicle controls. The incidences of adrenal gland medullary hyperplasia and focal hyperplasia of the adrenal gland capsule were also elevated in dosed male mice (NTP 1987).

Further analysis of the results of the NTP (1987) bioassay has raised certain questions as to the relevance of the observed renal tumors in male rats and hepatic tumors in mice to the potential carcinogenicity of 1,4-dichlorobenzene in humans. The observation that kidney tumors are induced in male but not female

rats in response to exposure to chemicals in addition to 1,4-dichlorobenzene has been the focus of recent research. Toxicologists at CIIT have hypothesized that the male rat kidney is susceptible to the induction of certain tumors because it contains the protein $\alpha_{2\mu}$-globulin, which has not been found at significant levels in female rats, or mice, or humans (Charbonneau et al. 1987, 1989a, 1989b; Olson et al. 1990). They have demonstrated that $\alpha_{2\mu}$-globulin in combination with compounds that bind reversibly with this protein enhances the formation of hyalin droplets in the proximal convoluted tubules of male rats. The resulting cellular damage and cell proliferation are hypothesized to result in enhanced tumor formation. Based on these considerations, EPA (1991i) and the Consumer Product Safety Commission have concluded that renal tumors only in male rats associated with $\alpha_{2\mu}$-globulin should not be used in assessing the potential carcinogenicity of 1,4-dichlorobenzene in humans.

There has also been much discussion of the interpretation of the finding of hepatocellular carcinomas and adenomas in mice in the NTP (1987) study. There was a higher than usual rate of these tumors in control female mice. Because 1,4-dichlorobenzene has not been demonstrated to be mutagenic in any of the microbial or mammalian systems tested, NTP (1987) has suggested that it may act as a tumor promoter by inducing DNA replication for tissue repair processes. As discussed previously, oral administration of 1,4-dichlorobenzene has been shown to increase DNA replication in the hepatocytes of mice (Steinmetz and Spanggord 1987a) and in the renal tissue of male rats (Charbonneau et al. 1989b; Steinmetz and Spanggord 1987b). These findings are consistent with the role of a promoter and suggest that 1,4-dichlorobenzene may not be a direct-acting carcinogen. Studies by Eldridge et al. (1992) and Umemura et al. (1996) suggest that cell proliferation may also play a role in the carcinogenic mechanisms of 1,4-dichlorobenzene.

The EPA Office of Drinking Water (EPA 1987a) has placed 1,4-dichlorobenzene into Category C (possible human carcinogen). This category is for substances with evidence of oncogenic potential in animal studies without supporting human data.

In an analysis of the NTP (1987) carcinogenicity data, EPA (1992) used the liver tumors in male mice and the linearized multistage model to calculate a q_1^* of 2.4×10^{-2} $(mg/kg/day)^{-1}$. Using the male rat kidney tumor data in the NTP (1987) study with 1,4-dichlorobenzene, Battelle and Crump (1986) report a q,* of 6×10^{-3} by the linearized multistage model, as well as by the multistage-Weibull and Grump's multistage models, taking time to death into account. Although the q_1^* for the male rat kidney tumors is lower than

that for the mouse liver tumors, EPA (1992) has decided to base estimates of risk on the mouse liver tumor data because the rat renal tumors are associated with $\alpha_{2\mu}$-globulin and hyalin droplet formation. Humans do not secrete $\alpha_{2\mu}$-globulin in their urine and are, accordingly, not susceptible to renal tumorigenesis by way of the hyalin droplet mechanism. Based on the q_1* of $2.4x10^{-2}$ $(mg/kg/day)^{-1}$ for liver tumors, oral doses associated with upper-bound risks of $l0^{-4}$, 10^{-5}, 10^{-6}, and $l0^{-7}$ would be 0.0042, 0.00042, 0.000042, and 0.0000042 mg/kg/day, respectively.

These values are currently under review by EPA and have not been included in the IRIS (1998) database. It is not likely, based on the potential for human exposure data presented in Chapter 5, coupled with the NOAELs and LOAELs gathered from human case reports and laboratory animal studies, that levels of 1,4-dichlorobenzene in the drinking water in any location would be high enough to cause a concern for cancer in humans.

2.6 CHILDREN'S SUSCEPTIBILITY

This section discusses the potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate due to maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on the developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between

children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to their body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

There is little credible scientific information available on the susceptibility and toxicological effects of 1,4-dichlorobenzene in children. The risk for exposure is apparently high. A study by Hill et al. (1995) measured blood levels of 1,4-dichlorobenzene and urine levels of its metabolites in 1,000 adults, finding that exposure to 1,4-dichlorobenzene was widespread, with 98% of the adults having measurable concentrations of 1,4-dichlorobenzene metabolites in their urine. There is no evidence to indicate that children are likely to be exposed to lower amounts of 1,4-dichlorobenzene from everyday living, suggesting that children are perhaps equally at risk for exposure and potential toxic side-effects.

Few studies have reported toxicological effects of 1,4-dichlorobenzene in children. Campbell and Davidson (1970) reported a case of a 21-year-old woman eating l-2 toilet air-freshener blocks per week while pregnant. The mother developed hematological aberrations (hypochromic, microcytic anemia, polychromasia); however, she delivered an apparently normal female infant with no apparent hematological problems. Because there are no known differences in the disposition of 1,4-dichlorobenzene in an adult's versus a child's body, it is anticipated that the health effects in the child and adult are similar, although there is no evidence to support this claim. Another study describes a 3-year-old boy who had been playing with crystals containing 1,4-dichlorobenzene for 4-5 days before being admitted to the hospital. On admission, the boy was jaundiced, his mucous membranes were pale, and he was diagnosed with anemia and methemoglobinemia. After a blood transfusion, the child gradually improved, but it was unclear whether the boy actually ingested any of the 1,4-dichlorobenzene (Hallowell 1959).

A two-generational study in pregnant rats exposed to 538 ppm 1,4-dichlorobenzene via inhalation produced decreased survival and decreased body weights in Fr pups (Tyl and Neeper-Bradley 1989). Murthy et al. (1987) reported morphologically abnormal sperm in rats exposed to 800 mg/kg/day by intraperitoneal injection. There are no studies that report transgenerational effects of exposure to 1,4-dichlorobenzene. By and large, most of the laboratory animal studies using rats, rabbits, and mice discussed earlier in this chapter have failed to yield significant toxicological effects on the male and female reproductive function or to produce adverse effects on the fetus (Hodge et al. 1977; Hayes et al. 1985; Giavini et al. 1986; Hollingsworth et al. 1956; Anderson and Hodge 1976; Riley et al. 1980; NTP 1987).

No studies are available that describe potential differences in the toxicokinetics or the mechanism of action of 1,4-dichlorobenzene in children. No data are available that specifically describe whether 1,4-dichlorobenzene or its major metabolites will cross the placenta. Because 1,4-dichlorobenzene is not known to be genotoxic, it poses no threat to the DNA in parental germ cells. No PBPK models are available for children, fetuses/pregnant women, or infants/lactating women exposed to 1,4-dichlorobenzene.

As discussed in Section 2.3, Toxicokinetics, the specific toxicokinetic behavior of 1,4-dichlorobenzene in children (and immature laboratory animals) has not been reported. Based on its physicochemical properties, it is anticipated that the absorption, distribution, metabolism, and excretion of 1,4-dichlorobenzene and its metabolites would be quite similar to that of the adult human (or animal), even when taking into account differences in body weight, total body water, body fat, volumes of distribution

(V_D), and perhaps lower activities of some metabolizing enzymes (cytochrome P-450) during the natal and neonatal periods. 1,4-Dichlorobenzene is a lipid-soluble toxicant and is likely to pass across the placental membranes. It will likely accumulate in many of the same tissues in the fetus that it would normally be expected to accumulate in the adult, with the possible exception of fat storage in the fetus (Li et al. 1995). Some amount of 1,4-dichlorobenzene accumulates in human breast milk (EPA 1983b), given its high lipid (milk fat) content, thereby providing a potential route of exposure to a nursing child, although there is no concrete data to support this relay exposure hypothesis. Some studies have noted that 1,4-dichlorobenzene will preferentially distribute to adipose tissues in relatively high amounts, compared to accumulations in the liver and kidneys (Hawkins et al. 1980; Charbonneau et al. 1989b; Klos and Dekant 1994). Loss of maternal body fat may potentially mobilize 1,4-dichlorobenzene from fat storage deposits in exposed mothers. This mobilization could result in increased blood levels and/or excretion of 1,4-dichlorobenzene and its metabolites from the mother, as well as redistribution to other fat deposition sites, such as the high fat content found in breast milk.

No studies have described the interactions of 1,bdichlorobenzene with other chemicals in children, or the means by which to reduce peak absorption of 1,4-dichlorobenzene after exposure.

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators of signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on

the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,4-dichlorobenzene are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,4-dichlorobenzene are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to 1,4-Dichlorobenzene

1,4-Dichlorobenzene can be measured in blood (Bristol et al. 1982; Langhorst and Nestrick 1979; Pellizzari et al. 1985) or adipose tissue (Jan 1983; Pellizzari et al. 1985), and its metabolite, 2,5-dichlorophenol, and/or its conjugates can be measured in urine (Langhorst and Nestrick 1979; Pagnotto and Walkley 1965) in order to confirm recent or prior exposure.

As discussed in Section 2.3, 1,4-dichlorobenzene may be present in blood for a limited time after exposure (Kimura et al. 1979). Therefore, measurement of 2,5-dichlorophenol in urine may provide a more reliable indication of 1,4-dichlorobenzene exposure since it can be excreted for several days (Hallowell 1959). Since 1,4-dichlorobenzene accumulates in fat, measurements of adipose concentrations of 1,4-dichloro-

benzene provide information on long-term exposure (Morita et al. 1975). Several chlorophenols, including 2,5dichlorophenol, have been identified in laboratory animals exposed to lindane. This indicates that the presence of 2,5dichlorophenol is fairly specific, but not completely specific, for 1,4-dichlorobenzene exposure. Information on the analytical methods commonly used to detect and quantify 1,4-dichlorobenzene in biological samples is presented in Section 6.1. There are currently no data available to assess a potential correlation between the values obtained with these measurements and the toxic effects observed in humans or laboratory animal species.

No information is available describing specific biomarkers of exposure to 1,4-dichlorobenzene in children.

2.7.2 Biomarkers Used to Characterize Effects Caused by 1,4-Dichlorobenzene

There are no known specific biomarkers of effects for 1,4-dichlorobenzene since none of the health effects identified in humans or animals appears to be uniquely associated with exposure to 1,4-dichlorobenzene. In oral studies using rats, characteristic effects have included increased enzyme activities at lower levels of exposure and porphyria at higher levels of exposure; in the kidneys of male rats, hyaline droplet formation accompanied by tubular degeneration has been seen at moderate-to-high levels of exposure. However, each of these effects can be seen as a consequence of exposure to a wide variety of chemicals.

Saito et al. (1996) studied the effect of oral treatment with 1,4-dichlorobenzene on the urinary excretion of kidney-type $\alpha_{2\mu}$-globulin (aG-K) in male Sprague-Dawley rats. Groups of 3 rats received placebo or 1,4-dichlorobenzene (1.5 mmol/kg/day; 220 mg/kg/day) by gavage in corn oil for 7 days. Concentrations of aG-K in the urine of 1,4-dichlorobenzene-treated rats ranged from 0.04 to 0.18 mg/mL; urine concentrations increased steadily throughout the study. In contrast, aG-K concentrations were undetectable in the urine of controls at all time points. The mean concentration of aG-K in the kidneys of rats treated with 1,4-dichlorobenzene was 1.15 mg/mg of soluble protein, compared to 0.35 mg/mg protein in the control group. The authors concluded that measurement of urinary aG-K would be a good indicator of 1,4-dichlorobenzene exposure; however, this response is neither unique to 1,4-dichlorobenzene nor applicable to human exposure cases. As discussed earlier in Section 2.5, this particular protein is produced in large amounts by male rats, accounting for 26% of their total urinary protein, but not in human males, where it was found to be present at 1% of the amount measured in male rats (Olson et al. 1990). Also, this protein is produced in only minimal quantities by females of any species or the males of other laboratory

species including mice (EPA 1991i). These observations have led to suggestions that humans are probably not at risk for the type of nephropathy induced by 1,4-dichlorobenzene in male rats, and that the $\alpha_{2\mu}$-globulin biomarker is inappropriate to use in humans (EPA 1991i).

No information was available describing specific biomarkers of effect in children to 1,4-dichlorobenzene. For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.8 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding the interactions of 1,4-dichlorobenzene with other chemicals. Because 1,4-dichlorobenzene is a liver toxin, it probably can interact with other chemicals that are liver toxicants. These toxicants are many, and include ethanol, halogenated hydrocarbons (chloroform, carbon tetrachloride, etc.), benzene, and other haloalkanes and haloalkenes. In addition, 1,4-dichlorobenzene toxicity may also be exacerbated by concurrent exposure with acetaminophen, heavy metals (copper, iron, arsenic), aflatoxins, pyrrolizidine alkaloids (from some types of plants), high levels of vitamin A, and hepatitis viruses. Such interactions could either be additive or synergistic effects.

Regarding its effect on hemolysis and formation of Heinz bodies, methemaglobinemia, and hemolytic anemia, it is likely that either additive or synergistic interaction would occur with other oxidants, such as aniline and acrolein, which are known to inhibit G6PD.

No information was available on interactions between 1,4-dichlorobenzene and other chemicals in children.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,4-dichlorobenzene than will most persons exposed to the same level of 1,4-dichlorobenzene in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of 1,4-dichlorobenzene, or

compromised function of target organs affected by 1,4-dichlorobenzene. Populations who are at greater risk due to their unusually high exposure to 1,4-dichlorobenzene are discussed in Section 5.7, Populations With Potentially High Exposure.

No population has been identified as exhibiting an unusual susceptibility to the effects of exposure to 1,4-dichlorobenzene. However, based on data from studies in humans and animals, individuals with compromised liver function, infants and children with immature liver function (Hallowell 1959), and elderly people (Cotter 1953; Nalbandian and Pearce 1965) may be more at risk than the general population. Individuals having a genetic susceptibility to methemoglobin formation (such as those individuals with a deficiency of G6PD in their red blood cells) may also be at increased risk from inhalation or oral exposure to 1,4-dichlorobenzene.

No information was available describing specific susceptibilities of children to 1,4-dichlorobenzene. There is no direct evidence that children differ in their susceptibility to the health effects of 1,4-dichlorobenzene from adults. This issue is discussed in detail in Section 2.6, Children's Susceptibility.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,4-dichlorobenzene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1,4-dichlorobenzene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

No information was available that described specific methods for reducing peak absorption following exposure, reducing body burden, interfering with the mechanism of action of toxic effects, or reducing toxic effects in children exposed to 1,4-dichlorobenzene. The following texts provide specific information about treatment following exposures to 1,4-dichlorobenzene:

Ellenhorn, MJ and Barceloux, DG, (eds.) (1988). Medical Toxicology: Diagnosis and Treatment of Human Poisoning. Elsevier Publishing, New York, NY.

Dreisback, RH, (ed.) (1987). Handbook of Poisoning. Appleton and Lange, Norwalk, CT.

Haddad, LM and Winchester, JF, (eds.) (1990). Clinical Management of Poisoning and Drug Overdose. 2nd edition, WB Saunders, Philadelphia, PA.

Grossel, TA and Bricker JD (1994). Principles of Clinical Toxicology. 3rd edition, Raven Press, New York. NY.

Aaron, CK and Howland, MA (eds.) (1994). Goldfrank's Toxicologic Emergencies. Appleton and Lange, Norwalk, CT.

2.10.1 Reducing Peak Absorption Following Exposure

Human exposure to 1,4-dichlorobenzene can occur by inhalation, ingestion, or dermal contact. General recommendations for reducing absorption of 1,4-dichlorobenzene following acute-duration inhalation exposure have included moving the patient to fresh air and administration of 100% humidified supplemental oxygen with assisted ventilation (HSDB 1996). General recommendations for reducing absorption following acute ingestion exposure have included inducing vomiting (unless the patient is or could rapidly become obtunded, comatose, or convulsing, and considering the risk of aspiration of vomitus), gastric lavage, or administration of a charcoal slurry (HSDB 1996). Intake of fatty foods which would promote absorption should be avoided. In the case of eye exposure, irrigation with copious amounts of water has been recommended (HSDB 1996). For dermal exposure, and to minimize dermal absorption, the removal of contaminated clothing and a thorough washing of any exposed areas with soap and water has been recommended (HSDB 1996).

2.10.2 Reducing Body Burden

1,4-Dichlorobenzene distributes to fatty tissues and is probably retained there at low concentrations (EPA 1986d; Hawkins et al. 1980; Morita and Ohi 1975; Morita et al. 1975). However, most of an absorbed dose is excreted within 5 days of exposure (Hawkins et al. 1980), and there is no evidence suggesting that the low levels of 1,4-dichlorobenzene that are likely to remain in fatty tissues would cause adverse effects. For these reasons, methods for enhancing elimination of 1,4-dichlorobenzene shortly after high-dose exposure could reduce toxic effects; however, no such methods have been identified. Methods that could enhance the elimination of 1,4-dichlorobenzene after high- or low-dose exposure in humans or laboratory animals have not been reported.

While it might be possible to develop methods to alter metabolism of 1,4-dichlorobenzene to promote formation of metabolites that are more easily excreted, this could be difficult because the current lack of knowledge of the specific metabolic pathways of 1,4-dichlorobenzene precludes speculation concerning which pathways it might be most beneficial to stimulate or inhibit. One pathway for which stimulation may be contraindicated is sulfate conjugate formation (Kimura et al. 1979). Methylation of 1,4-dichlorobenzene sulfate conjugates can occur, and these methylated conjugates are excreted less rapidly than nonmethylated conjugates (Kimura et al. 1979). Since little is known concerning the toxicity of these conjugates, it is presently not possible to determine the consequences of promoting formation of these metabolites.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action for liver effects of 1,4-dichlorobenzene has not been clearly delineated; however, based on *in vitro* experiments, induction of P-450 metabolism by pretreatment with phenobarbital may enhance hepatotoxicity (Fisher et al. 1991). This suggests that one mechanism of hepatotoxicity may be the production of reactive intermediates through phase I P-450-mediated oxidation, although it should be noted that the P-450 inhibitors metyrapone and SKF 525-A did not block hepatotoxicity of 1,4-dichlorobenzene in human liver tissue *in vitro* (Fisher et al. 1991). Lattanzi et al. (1989) provide evidence indicating that the microsomal mixed-function oxidase system and microsomal glutathione transferases and, to a lesser degree cytosolic glutathione transferases, can be involved in the bioactivation of 1,4-dichlorobenzene. More information concerning the mechanism of action for hepatic effects is needed before methods for blocking that mechanism and reducing toxic effects can be developed.

The mechanisms of action for nephrotoxic (with the exception of $\alpha_{2\mu}$-globulin-mediated nephropathy specific to male rats) or hematotoxic effects have not been clearly delineated, and with the available information, it is difficult to speculate how 1,4-dichlorobenzene might cause such effects. More information concerning the mechanisms of action for blood and kidney effects are needed before methods for blocking those mechanism and reducing toxic effects can be developed.

2.11 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate

information on the health effects of 1,4-dichlorobenzene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,4-dichlorobenzene.

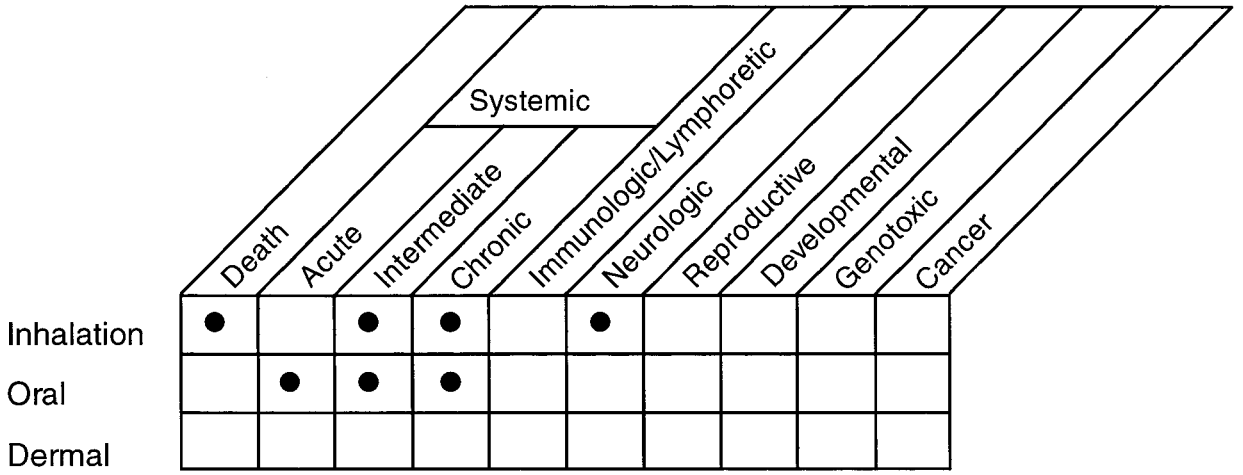
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.11.l Existing Information on Health Effects of 1,4-Dichlorobenzene

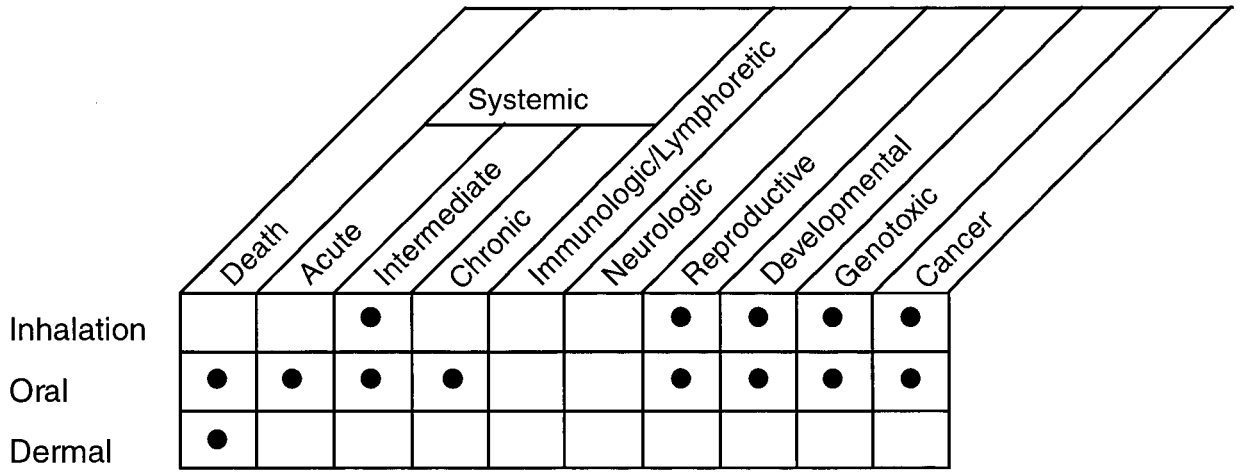
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,4-dichlorobenzene are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,4-dichlorobenzene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Some limited information (i.e., anecdotal, single acute-duration exposure, and workplace exposure) is available on the health effects of human exposure to 1,4-dichlorobenzene via inhalation and the oral route. For persons exposed via inhalation, there is information on death, systemic effects, neurologic effects, or the role of lifestyle factors resulting from intermediate- and chronic-duration exposure. There is also information on systemic effects in humans resulting from acute-, intermediate-, and chronic-duration oral exposure. It is important to note that most of this information was obtained from case studies in which levels and durations of exposure to 1,4-dichlorobenzene were unknown or uncertain.

Figure 2-4. Existing Information on Health Effects of 1,4-Dichlorobenzene



Human



Animal

● Existing Studies

The data available on 1,4-dichlorobenzene's health effects in animal studies are more extensive. Information is available on the developmental, reproductive, genotoxic, and carcinogenic effects of inhalation exposure to 1,4-dichlorobenzene, as well as on the systemic effects resulting from intermediate-duration exposure. In studies using oral exposure, information is available on death; systemic effects resulting from acute-, intermediate-, and chronic-duration exposure; and developmental, genotoxic, and carcinogenic effects. Only data on the lack of a lethal effect are available in studies using dermal exposure.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. The only information available for humans exposed to 1,4-dichlorobenzene for acute-duration exposure period is a case study of a 3-year-old boy who developed acute hemolytic anemia and methemoglobinemia after playing with and possibly ingesting 1,4-dichlorobenzene crystals (Hallowell 1959). Thus, he may have been exposed via the inhalation, oral, and dermal routes. The finding of methemoglobinemia in this child suggests that this may be an important end point for investigation in future animal studies with 1,4-dichlorobenzene via any route and for any duration of exposure. No studies that identified systemic toxicity in laboratory animals exposed to 1,4-dichlorobenzene via inhalation for this duration period were located. Several studies were conducted via the oral route including single-dose lethality studies in rats and guinea pigs (Hollingsworth et al. 1956): a 3-day study in rats that showed effects on the activities of some hepatic drug-metabolizing enzymes, a 5-day study in rats that resulted in porphyria (Rimington and Ziegler 1963), a 14-day study in rats that resulted in porphyria, a 14-day study in rats that resulted in increased activities of some microsomal xenobiotic metabolism systems (Carlson and Tardiff 1976), and two 14-day pilot studies in rats and two 14-day pilot studies in mice (NTP 1987). However, because a NOAEL for effects on hepatic enzymes was never identified and their relationship to overt hepatic lesions or deleterious health effects is not clearly understood, and because of uncertainty about the histopathological effects in mice and rats at the nonlethal exposure levels in the 16day pilot studies, the data are not considered sufficient to derive an acute-duration MRL for oral exposure, based on a hepatotoxicity end point. The data were sufficient to derive an acute-duration inhalation MRL of 0.8 ppm, based on a NOAEL of 300 ppm for lack of developmental effects in rabbits. Further studies of acute-duration are needed to establish the NOAEL and LOAEL for hepatic effects.

The only available study using the dermal route is a lethality study that attempted to determine a dermal LD_{50} level in rats (Gaines and Linder 1986). There are no available toxicokinetic data that have examined absorption of 1,4-dichlorobenzene via the dermal route. If dermal absorption and systemic distribution of 1,4-dichlorobenzene could be demonstrated, acute-duration studies using this route would be useful since humans are commonly exposed to it by handling various consumer products in the home and being exposed to the vapor form. Data on the effects of acute-duration exposure to 1,4-dichlorobenzene via inhalation would be extremely useful because inhalation of 1,4-dichlorobenzene by persons using consumer products containing it in the home and other indoor environments is the major route of exposure to this substance. In any further studies using the oral route, a broader range of dosage levels, including dosages lower than those used in currently available studies, would prove useful in order to determine a NOAEL. Any further studies conducted by any route should investigate hepatic, renal, central nervous system, and hematological (methemoglobinemia) effects as potential toxic end points. In addition, a recent study in which rats were given a single intraperitoneal injection of 1,4-dichlorobenzene resulted in abnormalities in sperm morphology (Murthy et al. 1987); therefore, any further acute-duration studies should assess this parameter. Further information on neurological effects resulting from acute-duration exposure would also be useful since these effects have been reported in several human case studies involving intermediate- and chronic-duration exposures (Campbell and Davidson 1970; Cotter 1953; Frank and Cohen 1961; Miyai et al. 1988).

Intermediate-Duration Exposure. Case studies are available on humans exposed to 1,4-dichlorobenzene via inhalation and the oral route for intermediate-duration exposure. These include the report of a 69-year-old man who developed skin discolorations and swelling of his hands and feet after about 3 weeks of exposure to 1,4-dichlorobenzene in his home (Nalbandian and Pearce 1965), the cases of a 60-year-old man and his wife who both died of liver atrophy after their home had been saturated with mothball vapor for 3-4 months (Cotter 1953), and the case of a 21-year-old woman who developed hypochromic, microcytic anemia as a result of ingesting 1,4-dichlorobenzene toilet air freshener blocks throughout pregnancy (Campbell and Davidson 1970). All of these case studies lack critical dosing amounts and durations, which makes it difficult to establish a dose-response curve for the toxicological effects in humans exposed to 1,4-dichlorobenzene. It would be helpful if future reports of accidental or intentional exposure would include more dose information (measured or estimated) so that dose-response relationships could be established (or at least reasonably estimated) for effects in humans.

Considerable data are available on the renal and hepatic effects of intermediate-duration inhalation exposure on a variety of laboratory animals (i.e., rats, mice, rabbits, guinea pigs, and monkeys) (Hollingsworth et al. 1956). These data were derived from a single large study with several inconsistent variables (discussed in Section 2.2.1.2). The data from the exposure of rats to concentrations of 1, 96, and 1.58 ppm showed enlargement and degeneration of hepatic parenchymal cells which were used as the basis of an inhalation MRL of 0.2 ppm (Hollingsworth et al. 1956). However, additional studies that follow current standards of good laboratory practice would be valuable for confirming these observations.

Several animal studies were located using the oral route for intermediate-duration and based on a combination of these studies, adverse effects have been reported in many organ systems. Hepatic, renal, and hematologic (Bornhard et al. 1988; Carlson 1977; Hollingsworth et al. 1956; NTP 1987) effects have been the most consistent observations. The MRL was based on a minimal LOAEL of 188 mg/kg/day based on increased liver weights in rats. Since kidney effects involve hyaline droplet nephropathy, the renal effects were not considered to be a suitable basis for the MRL.

Effects on hepatic enzyme systems have been reported at 1,4-dichlorobenzene levels far below those levels at which histopathologic effects were seen in other oral studies and a NOAEL for these enzyme effects has not yet been identified. In any further studies using the oral route, it would be useful to investigate potential histopathological effects at the low-dosage levels associated with effects on hepatic enzyme activities in order to identify NOAEL or LOAEL values. Some work has been done in this area pertaining to cell proliferation and a possible mechanism for hepatic neoplastic lesions observed in mice exposed to 1,4-dichlorobenzene (Eldridge et al. 1992; NTP 1987; Umemura et al. 1992). Further studies are needed to determine the relationship between cell proliferation and the cellular events that produce neoplasia in these animals and to determine more clearly the cancer risks to human health after exposure to 1,4-dichlorobenzene.

Studies using the dermal route for intermediate-duration exposure would be useful if absorption and systemic distribution of 1,4-dichlorobenzene by this route could first be demonstrated in toxicokinetic studies. In any further studies conducted for this duration period, methemoglobinemia, neurological effects, and effects on sperm morphology would be valuable.

Chronic-Duration Exposure and Cancer. Several case studies of chronic human exposure to 1,4-dichlorobenzene have been located. Reported effects resulting primarily from chronic inhalation exposure have included pulmonary granulomatosis in a 53-year-old woman who had been inhaling 1,4-dichlorobenzene crystals in her home for 12-15 years (Weller and Crellin 1953); atrophy and cirrhosis of the liver in a 34-year-old woman who was exposed to 1,4-dichlorobenzene-containing products in a small enclosed booth in a department store for one or more years (Cotter 1953); jaundice and liver atrophy in a 52-year-old man after 2 years of exposure to 1,4-dichlorobenzene in the fur storage plant where he worked (Cotter 1953); and ataxia, speech difficulties, limb weakness, and altered brainwave activity in a 25-year-old woman who had been exposed to high concentrations of 1,4-dichlorobenzene in her bedroom, bedding, and clothes for about 6 years (Miyai et al. 1988). A limited occupational health survey reported nasal and ocular irritation, but no major systemic health effects, were the only 1,4-dichlorobenzene-related complaints (Hollingsworth et al. 1956). Further occupational health data on individuals exposed chronically to 1,4-dichlorobenzene would be useful for both cancer and non-cancer health effect end points already mentioned. The only data located relating to chronic oral human exposure to 1,4-dichlorobenzene come from a case report of a 19-year-old black woman who developed an increase in skin pigmentation as a result of eating 1,4-dichlorobenzene moth pellets daily for about 2.5 years (Frank and Cohen 1961). All of these case studies lacked dosing amounts and durations, which makes it difficult to establish a doseresponse curve for the toxicological effects in humans exposed to 1,4-dichlorobenzene. No studies of chronic dermal exposure to 1,4-dichlorobenzene were located, although it seems likely that chronic inhalation and oral exposure scenarios, both in the home and in the workplace, have also involved dermal contact with 1,4-dichlorobenzene.

Available data on chronic exposure to 1,4-dichlorobenzene in animal studies include a 76-week inhalation study in rats that resulted in increased liver and kidney weights (Riley et al. 1980); a 2-year oral study in mice that resulted in liver effects (NTP 1987), such as hepatocellular degeneration, and cell necrosis and renal effects such as nephropathy and renal tubular degeneration; and a 2-year oral study in rats that resulted in a high rate of mortality and renal effects including nephropathy and degeneration of the renal tubules (NTP 1987). No animal studies of chronic dermal contact with 1,4-dichlorobenzene have been located.

The data were considered sufficient to derive a chronic-duration inhalation MRL of 0.1 ppm based on a NOAEL of 75 ppm for lack of hepatic effects (Riley et al. 1980). The database for oral exposure contains

two lifetime studies, one in rats and one in mice (NTP 1987). However, derivation of an MRL for chronic oral exposure does not appear to be justified because neither study identifies a clear NOAEL for all adverse effects. Hepatic effects were seen at the lowest dose tested in mice and renal effects at the lowest dose tested in rats.

Further data on the effects of chronic inhalation exposure to 1,4-dichlorobenzene would be useful, especially because chronic exposures to 1,4-dichlorobenzene in the air, in the home, and the workplace are the main sources of human exposure to this chemical. Any further testing of the effects of chronic exposure to 1,4-dichlorobenzene via the oral route should probably be done at lower levels of 1,4-dichlorobenzene than those that have already been used in the NTP (1987) bioassay, and should focus on doseresponse relationships involving the hepatic, renal, hematopoietic, central nervous system, and metabolic pathways. Data on the effects of chronic dermal exposure to 1,4-dichlorobenzene may be useful if dermal absorption and systemic distribution of 1,4-dichlorobenzene can be demonstrated from toxicokinetic studies, since chronic dermal exposure to 1,4-dichlorobenzene occurs as a result of bathing and showering in drinking water that contains low levels of this chemical in many U.S. communities. Any further testing by any route for duration should investigate the potential for methemoglobinemia, neurological effects, and effects on sperm morphology as possible end points.

No data have been located relating to carcinogenicity in humans exposed to 1,4-dichlorobenzene via inhalation, orally, or dermally. Epidemiological studies which used occupational exposure data would be useful to elicit such information on human exposure and potential cancer risks to 1,4-dichlorobenzene.

Animal data include a 76-week inhalation study in rats that did not result in cancer (Riley et al. 1980), a 2-year oral study in rats that resulted in renal cancer in males (NTP 1987), and a 2-year study in mice that resulted in liver cancer (NTP 1987). No data using the dermal route were located. Additional data via the inhalation route would be useful since chronic inhalation exposures to 1,4-dichlorobenzene in the air of the home and the workplace are the main sources of human exposure to this compound. No further studies via the oral route appear to be necessary at this time. Chronic-duration cancer studies via the dermal route may be useful since chronic dermal contact with 1,4-dichlorobenzene at low levels in drinking water occurs in several U.S. communities.

Genotoxicity. No studies were located regarding the potential genotoxic effects of 1,4-dichlorobenzene in humans exposed via inhalation, orally, or by the dermal route. Several *in vivo* studies in animals and *in vitro* studies are available that indicate that 1,4-dichlorobenzene is non-reactive with DNA and that the mechanism of carcinogenesis is that it acts as a tumor promoter rather than as a mutagen (Charbonneau et al. 1989b; Steinmetz and Spanggord 1987a, 1987b). There is no apparent need for further data in this area at this time.

Reproductive Toxicity. No information was located on potential reproductive effects in humans exposed to 1,4-dichlorobenzene via inhalation, orally, or by the dermal route.

Inhalation exposure to 1,4-dichlorobenzene did not appear to affect reproductive processes in rats except through its systemic toxicity in the dams (Tyl and Neeper-Bradley 1989). Although there were decreases in litter size, weight, and survival, these were considered to be the results of maternal toxicity. An inhalation study using male mice exposed to 1,4-dichlorobenzene for 5 days did not report an adverse impact on their ability to impregnate females (Anderson and Hodge 1976). In one study where male rats were intraperitoneally injected with 1,4-dichlorobenzene, there were increased incidences of morphologically abnormal sperm (Murthy et al. 1987); however, paternal effects were not noted in the 2-generation study (Tyl and Neeper-Bradley 1989). There were compound-related effects on the weights of the testes and ovaries or histopathological alterations in the mammary glands, testes, ovaries, and uteruses in rats exposed to 1,500 mg/kg/day for 13 weeks and only increases in relative ovary weights in mice exposed to 1,500 mg/kg/day for 13 weeks (NTP 1987). No treatment-related effects on the gross or histological appearance of the prostates, testes, uteruses, ovaries, or mammary glands were noted in a chronic study of both rats and mice exposed to doses up to 600 mg/kg/day (NTP 1987). Further data assessing the impact of 1,4-dichlorobenzene exposure on reproductive end points in both males and females exposed via the oral route would be useful. No studies were located that reported reproductive effects after a dermal route of exposure. Studies using the dermal route would also be useful if absorption and systemic distribution by this route could first be demonstrated by toxicokinetic studies.

Developmental Toxicity. No studies have been located that reported developmental effects on the offspring of humans exposed to 1,4-dichlorobenzene via the inhalation, oral, or dermal routes. Only one human case report mentioned the potential developmental effects of ingesting 1,4-dichlorobenzene at 38 weeks of gestation. The mother developed hematological effects due to 1,4-dichlorobenzene

consumption, but she did deliver a normal 4.3-kg female infant. Based on this one report, there appears to be little developmental toxicity of 1,4-dichlorobenzene in humans (Campbell and Davidson 1970); however, more information is clearly needed to confirm this observation in humans.

Animal data include an inhalation study in rabbits that resulted in an increased incidence of retroesophageal right subclavian artery in the fetuses (Hayes et al. 1985), and an oral study in rats that resulted in an increased incidence of an extra rib (NTP 1987). The data were considered sufficient to derive an acuteduration inhalation MRL of 0.8 ppm, based on a NOAEL of 300 ppm for lack of developmental effects in rabbits. It would be useful to have additional information on the developmental effects of 1,4-dichlorobenzene by inhalation and oral exposure in relation to maternal toxicity. There are currently no data available for the dermal route. Information on the developmental effects of dermal exposures would be useful if dermal absorption and systemic distribution of 1,4-dichlorobenzene could be demonstrated in toxicokinetic studies.

Immunotoxicity. No studies were located that directly assess the potential immunotoxic effects of 1,4-dichlorobenzene in humans exposed by inhalation, oral, or dermal routes. However, case reports of skin reactions in a 69-year-old man who was exposed via inhalation (Nalbandian and Pearce 1965) and a 19-year-old woman who ingested moth pellets (Frank and Cohen 1961) suggest that the immune system may be a target for 1,4-dichlorobenzene. Splenomegaly was noted in two people exposed to unknown amounts of 1,4-dichlorobenzene; however, it is unclear if the effect was chemical-related or due to another cause. Lymphoid necrosis in the thymus, lymphoid depletion in the spleen, and hematopoietic hypoplasia in the spleen and bone marrow were found in mice exposed to 1,500 mg/kg/day for 13 weeks and lymphoid depletion of the thymus and spleen in rats exposed for 13 weeks at 1,200 mg/kg/day (NTP 1987). The small amount. of available data suggest that immunological effects may be produced from exposure to 1,4-dichlorobenzene. In any future intermediate- or chronic-duration animal studies by any route of exposure, it would be useful to specifically assess the potential immunotoxic effects of 1,4-dichlorobenzene in both humans and laboratory animal models.

Neurotoxicity. Neurological effects including dizziness, weakness, headaches, nausea, vomiting, numbness, clumsiness, speech difficulties, and altered patterns of certain brainwaves have been reported to have occurred in case studies of persons exposed to 1,4-dichlorobenzene via inhalation (Cotter 1953; Miyai et al. 1988), as well as with other halogenated hydrocarbons. There are no data on neurological effects in

humans exposed to 1,4-dichlorobenzene through the oral or dermal routes. Neurotoxic effects of 1,4-dichlorobenzene in animals were only seen with inhalation exposures of adult rats to high doses (Tyl and Neeper-Bradley 1989). Tremors, weakness, and periods of unconsciousness were found in rabbits, guinea pigs, and rats exposed to 798 ppm of 1,4-dichlorobenzene for periods of 4 to 12 weeks (Hollingsworth et al. 1956). Similar neurological responses after oral doses of >770 mg/kg/day of 1,4-dichlorobenzene also have been reported (NTP 1987; Rimington and Ziegler 1963). Additional data on the neurological effects of 1,4-dichlorobenzene in animals exposed via inhalation and orally would be useful in confirming the effects reported in human case studies and in quantifying dose-response relationships. No studies were located that reported neurological effects after a dermal route of exposure. Studies using the dermal route would be useful if dermal absorption and systemic distribution were first demonstrated by toxicokinetic studies.

Epidemiological and Human Dosimetry Studies. The available literature that discusses human exposures to 1,4-dichlorobenzene is largely limited to individual case reports. These reports were of limited use because most did not estimate an exposure dose, with exposure times ranging from 1 day to 15 years. The limited information offered in these reports makes it difficult to construct a reliable doseresponse curve. Nonetheless, even though doses were not reported, some reports did suggest that upon inhalation or oral exposure to 1,4-dichlorobenzene, some of the same organ systems are affected in humans as in laboratory animals, particularly the hepatic and hematological systems (Campbell and Davidson 1970; Cotter 1953; Hallowell 1959). There are no available case studies or epidemiological data that suggest that levels of 1,4-dichlorobenzene found in the environment are associated with significant human exposure. The available data suggest that levels of 1,4-dichlorobenzene in outside air are relatively insignificant, although the compound is widespread (IARC 1982; Scuderi 1986; Wallace et al. 1986). Levels in groundwater and surface water are also relatively low (Coniglio et al. 1980; Dressman et al. 1977; IJC 1989; Oliver and Nicol 1982a; Page 1981; Staples et al. 1985). These observations indicate that the most likely population to exhibit the effects of 1,4-dichlorobenzene exposures would be occupationally exposed groups. Human epidemiological studies that provide a more definitive dose-response relationship between 1,4-dichlorobenzene exposure, clinical manifestations, and target organ toxicity (i.e., hepatic, hematological, and neurological systems) would be useful.

Biomarkers of Exposure and Effect.

Exposure. It is possible to measure 1,4-dichlorobenzene and its metabolite, 2,5dichlorophenol, in blood, adipose tissue, and urine (Bristol et al. 1982; Jan 1983; Kimura et al. 1979; Langhorst and Nestrick 1979; Pagnotto and Walkley 1965; Pellizzari et al. 1985). Additional data with which to correlate these measurements to exposure levels, particularly by the inhalation route, and the potential health effects, would be useful.

Effect. There are no health effects that are uniquely associated with exposure to 1,4-dichlorobenzene. Therefore, studies to identify a biomarker of effect for 1,4-dichlorobenzene would be useful.

Absorption, Distribution, Metabolism, and Excretion. There are no data on the toxicokinetics of 1,4-dichlorobenzene available from human studies. In the available case reports of human ingestion or inhalation of 1,4-dichlorobenzene, quantification of the doses is not possible. Experiments with laboratory animals show that 1,4-dichlorobenzene is absorbed via oral or inhalation exposure and is distributed mainly to adipose tissue, with some distribution to the liver and kidney, and minor amounts to other organs (Hawkins et al. 1980; Kimura et al. 1979). Absorbed 1,4-dichlorobenzene is principally metabolized to 2,5-dichlorophenol by oxidation and is rapidly eliminated, primarily in urine (Azouz et al. 1955; Hawkins et al. 1980), but also to some extent in the bile. There is extensive enterohepatic cycling. The available data indicate that the route of exposure has little effect on the subsequent metabolism and excretion of 1,4-dichlorobenzene. Scant data are available on absorption and systemic distribution resulting from exposure via the dermal route. 1,4-Dichlorobenzene produces a burning sensation when applied to the skin for a prolonged period of time, indicating at least minimal penetration to nerve endings within the skin (Hollingsworth et al. 1956). The little information that is available suggests that dermal exposure is associated with low systemic toxicity in both humans and laboratory animals. This information would be useful because it could provide the basis for assessing the probability of toxic effects resulting from dermal exposure and the need to conduct various toxicity studies via the dermal route. Additional toxicokinetic data would be useful to quantitate route-specific absorption rates. A physiologically based pharmacokinetic model would also be useful.

Comparative Toxicokinetics. There are no available studies that compare the toxicokinetics of 1,4-dichlorobenzene across species. This has been an important area of concern in interpreting the results

of animal studies with 1,4-dichlorobenzene with respect to their relevance to humans, most notably in the observations of renal toxicity and carcinogenicity in male rats. Although this specific issue has been largely resolved, it would be useful to have further data comparing the toxicokinetics of 1,4-dichlorobenzene across species in order to understand better which animal model is likely to compare most directly with humans with regard to other toxic effects in response to 1,4-dichlorobenzene exposure. From the available data in humans and laboratory animals, the primary metabolite produced after exposure to 1,4-dichlorobenzene is 2,5-dichlorophenol. This metabolite appears mainly in the urine after undergoing phase II metabolism, principally to the sulfate and glucuronide conjugates, with some exiting via the bile (Azouz et al. 1955; Fischer et al. 1995; Hissink et al. 1997; Hollowell 1959; Kimura et al. 1979; Klos and Dekant 1994).

Methods for Reducing Toxic Effects. Based on the chemical and physical properties of 1,4-dichlorobenzene, its absorption is most likely to occur by passive diffusion (see Chapter 3). However, this has not been investigated. Studies which investigate the mechanism by which 1,4-dichlorobenzene is absorbed may be useful in developing methods for reducing its absorption. Standard methods exist for reducing the absorption of 1,4-dichlorobenzene across the skin, lungs, and gastrointestinal tract (HSDB 1996) and are described in more detail in Chapter 6 of this profile; however, none of these are specific for exposures to 1,4-dichlorobenzene. 1,4-Dichlorobenzene can be retained in fatty tissues at low levels (EPA 1986f; Hawkins et al. 1980; Morita and Ohi 1975; Morita et al. 1975). Additional studies which characterize the metabolic pathways which enhance excretion may be useful in developing a method for reducing body burden. However, since most of the absorbed dose is eliminated within 5 days (Hawkins et al. 1980), it seems unlikely that methods for reducing body burden would be of much benefit. There is limited evidence that 1,4-dichlorobenzene is metabolically activated to hepatotoxic intermediates (Fisher et al. 1991; Lattanzi et al. 1989). Additional studies which further characterize the metabolic activation of 1,4-dichlorobenzene may be useful to understand how metabolites interact and to develop methods for interfering with the mechanism of action.

Children's Susceptibility. The majority of the data on the effects of exposure of humans to 1,4-dichlorobenzene has focused on adults. It is unknown whether children differ from adults in their susceptibility to health effects from 1,4-dichlorobenzene. Only two reports specifically referenced potential exposure to a child (Campbell and Davidson 1970; Hallowell 1959). Data relating to health effects in general for children are lacking. There are no data describing the developmental effects in

humans. Such data, although potentially useful, will be difficult to obtain. See the Developmental Toxicity subsection above for other data needs.

Although there is no reason to suspect that the pharmacokinetics of 1,4-dichlorobenzene differs in children and adults, scant data are available to support or disprove this statement. Studies of absorption, distribution, metabolism, and excretion in children would aid in determining if children are at an increased risk, particularly if conducted in an area where a high-dose acute or low-dose chronic exposure to an environmental source were to occur. With regard to exposure during development, additional research on maternal and fetal/neonatal toxicokinetics, placental biotransformation, the mechanism of action in children, and the risk associated with the transfer of 1,4-dichlorobenzene to an infant via breast milk would be useful in obtaining a more complete picture of prenatal and neonatal development. Direct evidence on whether 1,4-dichlorobenzene crosses the placenta and on the kinetics associated with that transfer is also needed. Data needs exist for determining if specific biomarkers of exposure or effect exist in children (and how those differ from adults) and how 1,4-dichlorobenzene interacts with other chemicals (i.e., other organochlorine pesticides, drugs, etc.) Lastly, data needs exist for methods to reduce peak absorption after exposure, to reduce body burden, and to interfere with the mechanism of action for toxic effects targeted for adults as well as for children.

Child health data needs relating to exposure are discussed in Section 5.8.1, Data Needs: Exposures.

2.11.3 Ongoing Studies

No known ongoing studies related to the toxicity or toxicokinetics of 1,4-dichlorobenzene were identified.